METHODS AND DEVICES FOR TRANSDERMAL DELIVERY OF ANTI-AGING COMPOUNDS FOR TREATMENT AND PREVENTION OF FACIAL OR NECK SKIN AGING

BACKGROUND OF THE INVENTION

Skin aging results from intrinsic and extrinsic processes. The innate or intrinsic aging process of the skin, called chronologic aging, is distinguished from changes resulting from actinic damage, which is mainly due to UV light, called photoaging. (Emerit, Free Radicals and Aging, Eds., I. Emerit & B. Chance, 1982, Birkhauser Verlag, Switzerland, incorporated herein by reference). Both processes are superimposed on sun-exposed parts of the body such as the hands and face.

Clinical morphological and biochemical characteristics of intrinsic and actinic aging processes are distinct. Various macroscopic and microscopic differences between the two processes have been described. (Gilchrest et al.,J. Invest. Dermatol. 80: 81-85, 1983; Kligman, Aging and the Skin, pp. 331-346, Eds. A.K. Balin and A.M. Kligman, 1989, Raven Press, New York; Montagna et al., J. Am. Acad. Dermatol.21: 907-918, 1989, each incorporated herein by reference). Macroscopically, intrinsic aging of the skin results in fine wrinkling, thinning and laxity of the skin, while photoaged skin displays a telangiectactic, leathery, dry, nodular surface with deep wrinkles, accentuated skin furrows, sags and bags. In addition, photoaged skin shows irregularities in pigmentation, actinic keratoses, as well as a variety of benign or premalignant growths. Microscopically, the dominant change in photoaging of the skin is the hyperplasia of elastic tissue in the dermis, which may lead to complete disorganization described as solar elastosis. In contrast, intrinsic aging induces only a modest increase in the number and thickness of the elastic fibers. Collagen undergoes only minor changes in intrinsic aging, while photoaging results in loss of collagen bundles, a decrease in mature collagen and an increase in type III collagen. The ground substance of the dermal matrix, which is composed of proteoglycans and hyaluronic acid, increases greatly in photoaged skin, while in protected skin the ground substance decreases with age.

Oxygen derived free radicals are generated in the skin from various sources and by various mechanism. In addition the skin is exposed to free radical generating environmental agents such as air pollutants and solar radiation. It is generally believed

that free radicals are responsible for at least part of the degenerative changes leading to cutaneous aging (Black, Photochem. Photobiol. 46: 213-221, 1987, incorporated herein by reference)

Hope for the successful treatment of intrinsic aging and photoaging of skin depends in part on the identification of therapeutic substances that can be effectively administered to patients to mediate or enhance skin protection and/or healing. One substance that has been reported as an effective agent against skin aging is a coenzyme designated "CoEnzyme Q". CoEnzyme Q is also known as ubiquinone on the basis that it occurs ubiquitously in biological systems. CoEnzyme Q is a quinone derivative with a long isoprenoid tail. The number of 5-carbon isoprene units in the coenzyme is variable. The most common form in mammals contains 10 isoprene units (CoEnzyme Q10, or CoQ10), but other forms contain up to 15 isoprene units (CoQ15). CoQ is the coenzyme for at least three mitochondrial enzymes (Complexes I, II, and III) as well as enzymes in other parts of the cell. These mitochondrial enzymes, which function in the oxidative phosphorylation pathway, are essential for the production of ATP, the energy source upon which all cellular functions depend. The biosynthesis of CoQ is known to be a multi-stage process requiring at least eight vitamins and several trace elements.

CoQ10 has been reported to yield beneficial therapeutic effects for many skin disorders, which effects may be attributed to antioxidant or free radical quenching properties of the coenzyme. Administration of CoQ10 reportedly reduces antioxidant damage to tissues and improves the immunocompetence of treated cells. These properties may be enhanced by administration of CoQ10 in combination with other nonenzymatic and enzymatic antioxidants. Based on a limited number of clinical trials, it has further been reported that CoQ10 works most effectively in the presence of certain vitamins and amino acids, including vitamins A, B6, C, D, and E, glutathione, carnitine, arginine, taurine, cysteine and methionine. Other ingredients may also significantly improve the therapeutic efficacy of CoQ10, for example the enzymes superoxide dismutase (SOD) and catalase, alpha-lipoic/dihydrolipoic acid, and proanthocyanadins.

Previous attempts to transdermally deliver protective substances such as CoQ10 and other anti-oxidants for therapeutic treatment to the skin, particularly to areas of the neck and face that are especially vulnerable to aging effects, have suffered from a number of important and confounding deficiencies. One important challenge that remains

is to provide improved medication patches that will continuously and evenly distribute medication to an extended surface area of the facial and neck skin. Conventional medication patches are also poorly adapted for comfortably and effectively delivering medication to the skin of the face or neck to treat facial or neck skin aging, particularly for an extended time period of treatment. In particular, conventional medication patches are not designed to conform to the contours and/or movements of facial or neck skin areas. Related to these deficiencies, conventional patches do not remain in effective contact with the skin of the face or neck for an extended period of time for controlled, extended release of medication from the patch to the skin of the face or neck. Additional drawbacks of available transdermal patch delivery devices and methods point to a need for improved pharmaceutical formulations and methods for administering protective substances, such as anti-oxidants, that are stable and well tolerated and that provide enhanced delivery and bioavailability to facial and neck skin areas.

SUMMARY OF THE INVENTION

The present invention fulfills the foregoing needs and satisfies additional objects and advantages by providing novel, effective devices, methods, and compositions for preventing and treating facial and neck skin aging in a mammalian subject, typically a human subject. In various alternative embodiments of the invention a partial or complete facial or neck skin patch or mask is provided that comprises a flexible patch or mask body formed of a porous material. The patch or mask body is sized and dimensioned to conform to one or more contoured facial and/or neck skin areas of a subject to be treated for prevention or reversal of skin aging. The patch or mask of the invention further comprises attachment means connected to the patch or mask body for securely attaching the patch or mask in contact with one or more contoured facial and/or neck skin areas of the subject. One or more anti-aging effective compound(s) is/are applied to, or otherwise provided in chemical communication with, an undersurface of the patch or mask body to effectuate delivery of the anti-aging compound to the contoured facial and/or neck skin area in an effective amount, and for an effective period of time, to prevent or alleviate symptoms of skin aging in the facial and/or neck skin area to which the patch or mask is applied.

In other embodiments, the invention provides a facial and/or neck patch or mask for enhanced delivery of an anti-aging effective compound to a facial and/or neck

skin area of a mammalian subject to treat or prevent skin aging in the subject. The facial and/or neck patch or mask comprises a flexible patch or mask body formed of a porous material. The patch or mask body is sized and dimensioned to conform to one or more contoured facial and/or neck skin area(s) of the subject, such as an orbital margin, nasal skin area, labial margin, mandibular, maxillary, or temporal facial skin area, chin, jowl and/or neck skin area of the subject. Flexibility of the facial and neck patches and masks allows conformity and stretching of the patch or mask in conjunction with normal facial and neck skin movements, as occur during jaw flexure, head turning, and eye opening and closure. Accordingly, the patch or mask body is typically constructed for expansion and/or elastic flexure in all directions planar to an undersurface of the patch or mask that is applied to the facial or neck skin area to be treated. An attachment means is connected to the patch body for securely attaching the patch in contact with the facial and/or neck skin area(s) to be treated. An anti-aging effective compound is provided in contact with an undersurface of the patch body, which is adapted for enhanced delivery and bioavailability of the anti-aging compound to a facial and/or neck skin area to prevent or alleviate symptoms of skin aging in the area(s) to which the patch or mask is applied.

In further embodiments of the invention, a method for treating facial and/or neck skin aging is provided that involves applying a facial or neck patch or mask to a facial or neck skin area in a mammalian subject. The patch or mask comprises a flexible patch body formed of a porous material sized and dimensioned to conform to one or more contoured facial and/or neck skin area(s) of the subject, such as an orbital margin, nasal margin, labial margin, or jowl skin area of the subject. The patch or mask is applied to the subject facial and/or neck skin area(s) and removably secured thereto by an attachment means connected to the patch body for securely attaching the patch in contact with the facial skin area(s) to be treated. The methods of the invention further include delivering an anti-aging effective compound to the facial skin and/or neck skin area(s) to be treated from an undersurface of the patch or mask body after the patch or mask has been applied, to yield enhanced delivery and bioavailability of the anti-aging compound to the underlying facial and/or neck skin to prevent or alleviate one or more symptoms of facial skin aging. In more detailed aspects, the methods of the invention yield controlled, time-release delivery of the anti-aging compound. In other detailed aspects of the invention, a second anti-aging effective compound is coordinately delivered with patch- or mask-mediated administration of the first anti-aging effective compound. Typically, the second anti-aging

effective compound is formulated in combination with the first anti-aging effective compound and coordinately delivered via the facial patch or mask, as described above. Alternatively, the second anti-aging effective compound may be topically applied or otherwise coordinately delivered to the facial and/or neck skin area to be treated before or after application of the patch or mask.

In more detailed aspects of the invention, the facial patch or mask comprises an orbital patch or mask for treatment of periorbital skin aging in a mammalian subject. The orbital patch or mask comprises a flexible patch or mask body formed of a porous material, wherein the patch or mask body is sized and dimensioned to conform to an orbital margin of the subject. An attachment means is connected to the patch or mask body for securely attaching the patch or mask in contact with the orbital margin of the subject. An anti-aging effective compound is applied to or otherwise provided in contact with an undersurface of the patch or mask body. The undersurface of the patch or mask body is adapted for effective delivery of the anti-aging compound to the orbital margin of the subject for a period of time effective to prevent or alleviate symptoms of periorbital skin aging.

In additional detailed aspects, an orbital patch or mask is provided as above that conforms to one or more selected portions of the orbital margin of the subject. Thus, the patch or mask may conform to one or more areas of the orbital margin selected from the supraorbital margin, infraorbital margin, lateral orbital margin and/or medial orbital margin of the eye. In related aspects, the orbital patch or mask may comprise one or more separate or conjoined, countoured sections individually shaped and dimensioned to conform to a selected portion of the orbital margin, for example one or more sections conforming collectively or individually to a lenticular area of the supraorbital margin, a lenticular area of the infraorbital margin, a medial orbital margin, and/or a lateral orbital margin. These sections may be provided as individual patches, or the sections may be conjoined in a single patch or mask having a unitary body or interconnecting member(s) joining the individual sections in an anatomically integrated array of sections.

The orbital patches and masks of the invention are flexible and designed to conform closely to the skin of the orbital margin of the subject, to effectively and evenly deliver an anti aging effective compound to the periorbital skin area to be treated. In related aspects, the anti-aging effective compound is provided in a delayed release

formulation to provided extended, controlled release of the anti-aging compound for a period of time effective to prevent or reverse one or more symptoms of periorbital skin aging in the subject. The ocular patches of the invention are typically constructed to ensure that the anti-aging effective compound is delivered to the orbital margin while avoiding exposure of the compound and other potentially irritating carriers and materials to the mucus membrane of the eye.

In additional detailed embodiments, the invention provides a nasal patch or mask for treatment or prevention of perinasal skin aging in a mammalian subject. The nasal patch or mask comprises a flexible patch or mask body formed of a porous material sized and dimensioned to conform to a nasal skin surface or portion thereof (e.g., a lateral nasal margin) of the subject. An attachment means is connected to the patch or mask body for securely attaching the patch or mask covering the nose or in contact with a nasal margin of the subject. An anti-aging effective compound is applied to, invested in, or otherwise provided in contact with an undersurface of the patch or mask body. The undersurface is adapted for effective delivery of the anti-aging compound to the nose or nasal margin for a period of time effective to alleviate symptoms of perinasal skin aging.

In other embodiments, the invention provides a labial patch or mask for treatment or prevention of perilabial skin aging in a mammalian subject. The labial patch or mask comprises a flexible patch or mask body formed of a porous material sized and dimensioned to conform to a labial margin of the subject. An attachment means is connected to the patch or mask body for securely attaching the patch or mask in contact with the labial margin of the subject. An anti-aging effective compound is provided in contact with an undersurface of the patch or mask body. The undersurface is adapted for effective delivery of the anti-aging compound to the labial margin for a period of time effective to alleviate symptoms of labial skin aging.

In yet additional embodiments, the invention provides a neck patch or mask for treatment or prevention of aging symptoms in the skin of the neck and/or under the chin in a mammalian subject. The neck patch or mask comprises a flexible patch or mask body formed of a porous material. The patch or mask body is sized and dimensioned to conform to one or more skin area(s) of the neck and/or face, for example covering one or more of the sides of the neck, the throat, and/or under the chin of the subject. An attachment means is connected to the patch or mask body for securely attaching the patch

or mask in contact with the neck and/or facial skin surface(s). An anti-aging effective compound is provided in contact with an undersurface of the patch or mask body. The undersurface is adapted for effective delivery of the anti-aging compound to skin of the neck for a period of time effective to alleviate symptoms of neck and/or facial skin aging.

In more detailed aspects of the invention, the facial or neck patch or mask comprises a flexible patch or mask body comprising a self-supporting sheet, pad, or matrix of porous material. The patch or mask body is often formed of a water insoluble material, commonly a polymeric material, providing suitable strength, integrity, and comfort for use as a facial (e.g., ocular) patch or mask. Typically, the patch or mask body, or at least an undersurface portion thereof, serves as a substrate or reservoir for receiving and retaining the anti-aging effective compound, which may be formulated in a variety of pharmaceutical delivery vehicles or carriers. The anti-aging effective compound may be applied directly to the undersurface of the patch or mask body, or may be absorbed, adsorbed, or otherwise admixed with or invested in the material of the patch body at the undersurface and/or within the porous patch or mask body in communication with the undersurface (e.g., by liquid or other direct chemical communication between the body and the undersurface through pores, fissures, perforations, or other communication channels provided within the patch body or a layer thereof adjacent the undersurface). In exemplary embodiments, the flexible patch body comprises a natural or synthetic fiber or polymer such as cotton, cellulose, nylon, polyester, or polyacetate polymer.

In additional detailed aspects of the invention, the attachment means for attaching the facial patch or mask to the facial skin area(s) to be treated comprises a bioadhesive material such as a hydrogel. Optionally, the bioadhesive material is a bioadhesive delivery vehicle that serves a dual purposes of mediating affixation of the patch or mask to the facial skin area(s) and providing a carrier or delivery vehicle for incorporation and delivery of the anti-aging effective compound(s). In other embodiments, the bioadhesive delivery vehicle is connected to a periphery of the undersurface of the patch or mask body, for example to the periphery of the undersurface of an ocular patch.

In certain embodiments of the invention, the anti-aging effective compound employed with the facial patch or mask comprises an anti-oxidant compound. Exemplary anti-oxidants for use within this aspect of the invention include anti-oxidant coenzymes, for example "Coenzyme Q" coenzymes. Alternatively, anti-oxidants for use within the

invention are selected from vitamins, amino acids, enzymes, and/or fatty acids. In additional embodiments, a second anti-aging effective compound, for example a second anti-oxidant compound, is delivered coordinately with patch- or mask- mediated delivery of a first anti-oxidant compound. The second anti-aging compound may be formulated in combination with the first anti-aging compound and applied or otherwise provided in contact with the undersurface of the patch or mask. Alternatively, the second anti-aging compound may be administered, e.g., as a topical formulation, to the facial skin area to be treated prior to or subsequent to application and removal of the patch or mask. In further detailed embodiments, the facial patch or mask provides controlled, time-release delivery of one or more anti-aging effective compound(s), typically for a prolonged time period of 1-4 hours, 4-8 hours, or more than 8 hours effective to prevent or reverse one or more symptoms of facial skin aging in the subject.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a perspective view of a human female subject wearing a variety of facial and neck patches and masks of the invention.

Figure 2 is a perspective view of a human female subjectshowing various anatomical features that relate to novel configurations of the facial and neck patches and masks of the invention.

Figure 3 is a perspective view of a human female subject wearing alternate embodiments of facial masks of the invention.

Figure 4 is a perspective view of a human female subject wearing additional alternate embodiments of facial masks of the invention.

Figure 5 is an isometric view toward the undersurface of an orbital patch of the invention having multiple drug delivery sections.

Figure 6 is an isometric view toward the undersurface of a composite orbital patch of the invention having multiple drug delivery sections.

Figure 7 is a sectional view of an orbital mask of the invention illustrating alternate features thereof.

Figure 8 is a sectional view of a facial patch of the invention illustrating alternate features thereof.

Figure 9 is a sectional view of a facial patch of the invention including a thermal element.

Figure 10 is a sectional view of a facial patch of the invention including a thermal element.

Figure 11 is a sectional view of a facial patch of the invention illustrating alternate features thereof.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the invention provides a variety of novel facial patches 10 and masks 12 for treating facial skin aging in mammalian subjects, typically human subjects (Fig. 1). The facial patch or mask comprises a flexible patch body 14 formed of a porous material, wherein the patch or mask body is sized and dimensioned to conformto one or more contoured facial surfaces of the subject, for example an orbital margin, nasal skin surface, or labial margin. The patch or mask includes attachment means 16 connected to the patch or mask body for securely, removably attaching the patch in contact with the facial surface to be treated. An anti-aging effective compound is provided in contact with an undersurface 18 of the patch body that is in turn adapted for effective delivery of the anti-aging compound to the facial skin surface when the patch or mask is applied thereto.

In certain detailed aspects, the invention provides a facial patch 10 or mask 12 or a neck skin patch or mask 146 for prophylaxis and treatment of one or more symptoms of facial and/or neck skin aging (e.g., photoaging oractinic aging, and chronological aging), including symptoms selected from:

a) Degeneration of the microvascular system;

b) Flaccidity and development of wrinkles due to a decrease in and/or crosslinking of collagen, accumulation of glucosaminoglycans (base substance) and/or solar elastosis (elastin clumping);

c) Flattening of the retial cones, associated with a reduction in thickness or area between the dermis and epidermis through which substances are exchanged for healthy metabolism of the epidermis;

d) Restricted regenerative turnover in the epidermis associated with defective hornification, leading to drying out of the skin, roughness of the skin, chapping of the skin and/or flaking;

e) Defective regulation of cell division (proliferation) and cell maturation (differentiation) in the epidermis associated with cellular atypia, atrophies, and loss of polarity; and/or

f) Local hyper- and hypopigmentation and/or abnormal pigmentation (age spots).

The invention thus provides novel facial patches 10 and masks 12 for use in the prevention or treatment of one or more symptoms of facial skin aging. The patch or mask body 14 is typically comprised of a flexible, porous self-supporting material that provides strength, comfort and integrity for use as a facial skin patch. The patch body is shaped and dimensioned to conform to a contoured skin surface of the face, and the mask body is shaped and dimensioned to conform to a plurality of contoured skin surfaces of the face. In exemplary embodiments, the patch or mask body is formed of a water insoluble fiber or polymer. In additional aspects, the patch or mask body provides a substrate or reservoir for receiving and retaining an anti-aging effective compound, which may be formulated in a variety of pharmaceutical or cosmetic carriers or delivery vehicles, such as a polymeric delivery vehicle. The anti-aging effective compound is applied to, admixed with, invested in, or otherwise provided in contact with at least the undersurface 18, or a portion thereof (e.g., a peripheral portion of the undersurface) of the flexible patch or mask body, to yield sustained transdermal delivery of the anti-aging effective compound to the facial skin area to be treated.

In certain detailed embodiments of the invention, the flexible patch 10 or mask 12 body 14 comprises a lightweight, flexible strip, pad or a partial or complete mask of biologically compatible material, for example a woven or nonwoven fiber or polymer material, such as polyester, cotton, cellulose, or nylon fibers. Exemplary materials include porous polymeric water insoluble nonwoven fibrous fabrics. The fiber or polymer may be complexed, cross-linked or bonded into a porous fabric or matrix, for example by binding of individual fibers into a fabric using a sizing resin. Suitable sizing materials for bonding fibers within the patch or mask body include latex resins.

The flexible patch 10 or mask 12 body 14 is generally nonirritating to human skin. If desired, the patch or mask body can be coated on one or more surfaces with a release coating, such as a silicone release coating as described in U.S. Pat. No. 4,696,854 which is incorporated herein by reference. A suitable release coating in this context is a 100% solids electron beam curable silicone such as Tego® (Silicone Resin Acrylates/RC-Series RC 705 and RC 726 by Goldschmidt Chemical Corporation, Hopewell, Va).

In exemplary embodiments of the invention, the flexible patch 10 or mask 12 body 14 comprises a stable, water insoluble flexible material. For example, the body may be constructed of a suitably thin (e.g., approximately 1mm to 1 cm thick) strip, pad or sheet of nonwoven fabric formed from one or more selected fibers (e.g., cellulose fibers derived from wood pulp and/or polyester fibers). When fibrous materials are used, the fibers may be assembled loosely to form the patch or mask body and to maintain porosity thereof. A unifying or sizing resin may be applied to hold the fibers together. The sizing resin can comprise a nonirritating resin such as a latex emulsion. One suitable resin emulsion adhesive is Hycar® 26477 (B. F. Goodrich Co., Brecksville, Ohio). Another suitable material for construction of the patch or mask body is a nonwoven fabric comprising a wetlay cellulose and polyester containing as a sizing resin an acrylic latex emulsion (Dexter Corporation, Windsor Locks, Conn.)

Within additional embodiments of the invention, the flexible patch 10 or mask 12 body 14 comprises a porous woven acetate polymer cloth, sometimes known as "silk cloth."

Yet another suitable material for construction of the flexible patch 10 or mask 12 body 14 is an open-cell plastic foam strip, sheet, pad, or partial or complete mask. In exemplary embodiments, the patch or mask body is formed of a low density polyethylene or polyvinyl acetate resin. Alternatively, woven cotton cloth, or synthetic cloths such as nylon, polyester, polyacetate, and the like may be employed. When the flexible patch or mask body is a woven cloth, no sizing resin is needed.

The flexible patch 10 or mask 12 body 14 is typically pervious to air so that the patch or mask is non-occlusive to the skin and allows moisture to pass from the treated skin surface through the patch or mask body into the atmosphere. The moisture vapor transmission rate (MVTR) of normal facial skin under various conditions is typically from about 70 to about 150 $g/m^2/24$ hr, and the facial patch or mask of the present invention allows for transmission of moisture vapor from the skin through the patch or mask body at a rate of at least from about 35 to about 75 $g/m^2/24$ hr, and more typically from about 70 to about 150 $g/m^2/24$ hr or greater. Conventional medication-applying patches that employ a rubber backing or other occlusive construction materials adversely limit moisture evaporation from the skin. By contrast, when non-occlusive materials are employed within the patches and masks of the present invention, the patch or mask will not

substantially interfere with moisture evaporation from the skin. This is importantbecause the evaporation of moisture from the skin helps the skin to act in its normal capacity as a barrier to externally applied compounds that, if absorbed in excessive amounts, can produce toxic reactions or skin irritation. The invention thus enables the barrier function of the stratum corneum to be maintained while providing for effective delivery of the anti-aging compound(s) to the treated skin area(s).

The porosity of the flexible patch 10 or mask 12 body 14 also provides openings, pores, and/or channels 20 infiltrating at least a portion of the patch or mask body adjacent the undersurface 18 thereof, wherein the openings, pores, and/or channels are adapted for receiving and controllably releasing the anti-aging effective compound(s). These openings, pores and/or channels provide a reservoir for prolonged, controlled delivery of the anti-aging effective compound(s) from the undersurface of the patch or mask to the facial skin area to be treated. The openings, pores and/or channels are in chemical communication with the undersurface of the patch or mask body. For example, the anti-aging effective compound can enter and/or leave the openings, pores and/or channels via chemical communication facilitated by diffusion, capillary transport, wicking, and/or decompression and compression transfer. In this manner, the anti-aging effective compound can be initially applied, loaded or infused within the openings, pores and/or channels of the patch or mask body and subsequently released to the undersurface ina controlled manner to yield efficient, optionally time-release-controlled, delivery of the anti-aging effective compound to the facial skin area(s) to be treated.

Various methods and carriers are provided within the invention for applying the anti-aging effective compound(s) to the undersurface 18 of the patch 10 or mask 12, and/or for loading or infusing the anti-aging effective compound(s) within the openings, pores and/or channels 20 of the patch body 14. For example, application of the anti-aging effective compound onto the undersurface of the patch or mask body can be achieved by simple, known and optionally mechanized processes of aliquoting the anti-aging effective compound (optionally combined in a pharmaceutical or cosmetic carrier or delivery vehicle) onto the undersurface in an appropriate (therapeutically or prophylactically effective) concentration and amount to achieve an even distribution of the compound over the portion(s) of the undersurface to be coated. Alternatively, the anti-aging compound and optional carrier can be imbued within at least a portion of a porous polymeric or

fibrous patch or mask body (e.g., a portion of the body adjacent the undersurface, to a predetermined depth or thickness of the body) facilitated by various know, methods, including surface application coupled with diffusion, capillary transport, wicking, and/or decompression absorption. In certain detailed embodiments, the anti-aging compound is incorporated within at least a portion of the patch or mask body during its manufacture, for example by infusing a pressure-sensitive polymeric delivery vehicle containing the anti-aging effective compound into a polymeric patch or mask body by controlled manufacture methods (as disclosed, e.g., in U.S. Patent No. 6,096,334, incorporated herein by reference) to facilitate penetration of the anti-aging compound and carrier into the patch or mask body.

In related aspects of the invention, the anti-aging effective compound is provided in a delayed release formulation to provide extended, controlled release of the anti-aging compound to yield delivery of the compound to a targeted facial skin area for treatment for a period of time effective to prevent or reverse one or more symptoms of facial skin aging in the subject.

In additional aspects, the anti-aging effective compounds are formulated in a polymeric delivery vehicle or other pharmaceutical or cosmetic carrier that allows penetration of the anti-aging effective compound into a substantial portion of the flexible patch or mask body. For example, the anti-aging effective compound may be formulated and imbued, infiltrated, or otherwise invested within the patch 10 or mask 12 body 14 to penetrate from the undersurface 18 into openings, pores and/or channels 14 to at least about one-fourth or one-half of a depth or thickness 22 of the patch or mask body. More typically the anti-aging effective compound is formulated and invested within the patch or mask body 10 to penetrate from the undersurface into openings, pores and/or channels that infiltrate at least about one-half, three-quarters, and up to the full depth or thickness of the patch body.

In certain detailed aspects of the invention, an orbital facial patch 24 (Fig. 1) or orbital mask 26 (Fig. 3) is provided for prevention or treatment of periorbital skin aging. The orbital patch or mask anatomically conforms to, and provides for treatment or prevention of skin aging in, all or part of an orbital margin 30 skin area, and optionally in the case of a mask to one or more adjoining skin area(s). The orbital patch or mask comprises a flexible patch or mask body 14 formed of a porous material, wherein the patch

or mask body is sized and dimensioned to conform to all or part of an orbital marginal skin surface of the subject, and optionally to one or more additional facial skin area(s), such as a nasal skin area. An attachment means 16 is connected to the orbital patch or mask body for securely attaching the patch or mask in contact with all or part of the orbital margin 30 (Fig. 2) of the subject. An anti-aging effective compound is applied to or otherwise provided in contact with an undersurface of the patch or mask body. The undersurface of the patch or mask body is adapted for effective delivery of the anti-aging compound to all or part of the orbital margin of the subject for a period of time effective to prevent or alleviate symptoms of periorbital skin aging.

Various shapes and configurations of orbital facial patches 24 and masks 26 are provided, including patches and masks that conform to the all or part of the orbital margin(s) 30 of one or both eyes 32 of the subject, and optionally to one or more additional facial skin area(s) (see, Fig.s 1-3). For example, as shown in Fig. 1, a crescent shaped or lenticular supraorbital patch 34 is provided that conforms to a supraorbital margin 36 of the eye, generally demarcated above a transverse plane bisecting the eye and below the crescent-shaped eyebrow 38, optionally including all or part of the upper eyelid 40. Often, the skin area of the supraorbital margin that is covered by a supraorbital patch of the invention is generally a lenticular (lens-shaped) area of skin that excludes the most lateral and medial corners 42, 43 of the supraorbital margin, and the patch is correspondingly shaped and dimensioned, to prevent discomfort to the subject and/or creasing of the patch in these spatially confined areas prone to muscular contortion and/or skin folding. Orbital patches applied in this configuration nonetheless effectively treatthe entire supraorbital skin by providing effective delivery to skin areas beyond the patch margins.

In related embodiments, an infraorbital eye patch 44 is provided that is shaped and dimensioned to substantially cover an infraorbital margin 46 skin surface surrounding the eye 32 below a horizontal plane bisecting the eyeball, optionally including all or part of the lower eyelid 48 (Fig.s 1 and 2). As in the case of the supraorbital patch 34, the infraorbital marginal skin area covered by the infraorbital patch is often generally lenticular in shape and excludes the most lateral and medial corners of the infraorbital margin, and the patch is correspondingly lenticular shaped and dimensioned.

In additional related embodiments, as exemplified in Fig. 1, a lateral orbital patch 50 is provided that is shaped and dimensioned to substantially cover a lateral orbital margin 52 of the subject--the site where aging symptoms commonly referred to as "crows feet" appear. As is also depicted in Fig. 1, a lateral orbital patch may be generally circular, ovate, or fan-shaped to substantially conform to the lateral orbital margin, comfortably and without peripheral impingement of the patch against a coordinately applied supraorbital patch 34 or infraorbital patch 44.

In further related embodiments, as exemplified in Fig. 1, a medial orbital patch 56 is provided that is shaped and dimensioned to substantially cover a medial orbital margin 58 of the subject. The medial orbital patch may also be generally circular, ovate, or fan-shaped to substantially conform to the medial orbital margin, comfortably and without peripheral impingement of the patch against a coordinately applied supraorbital patch 34 or infraorbital patch 44.

In other related embodiments, orbital patches 24 and masks 26 are provided that substantially conform to one, or to a plurality of, selected portions of the orbital margin 30 of the subject, up to and including an entire orbital marginal area, of one or both orbital margins of the subject. In more detailed aspects, the patch 24 or mask 36 may conform to one or more areas of the orbital margin selected from the supraorbital margin 36, infraorbital margin 46, lateral orbital margin 52, and/or medial orbital margin 58 of one eye 32, or of both eyes.

In related aspects, the orbital patch 24 or mask 26 body 14 may comprise one or more separate or conjoined, contoured sections individually shaped and dimensioned to conform to one or more selected portions of one or both orbital margin(s) 30 of the subject. For example, referring to Fig.s 2 and 4, the orbital patch or mask may comprise one or more specially contoured and/or constructed drug delivery sections of the body that conform, collectively or individually, to all or part(s) of the surface(s) of the supraorbital margin 34, the infraorbital margin 46, lateral orbital margin 52, and/or medial orbital margin 58 of one or both eye(s). Patches constructed in this manner can cover and effectively deliver the anti-aging compound to any one or more of these portions of the orbital margin, and may comprise one, two, three, four or more sections, for example selected from a supraorbital section 62, infraorbital section 64, lateral orbital section 66 and/or medial orbital section 68. In other embodiments, multiple sections of an orbital

patch will each cover and deliver medication to a plurality of skin portions of the orbital margin, for example a supraorbital section 62 and lateral orbital section 66, or a infraorbital section 64 and medial orbital section 68.

Individual orbital patch 24 sections may be conjoined in a single patch having a unitary body (e.g., as shown in Fig.s 4 and 5). Alternatively, the sections may be joined by interconnecting member(s) 60 (e.g., as shown in Fig. 6) joining one or more individual sections in an anatomically integrated array of sections. The interconnecting member(s) can be constructed of the same material as the patch sections that form the sectional patch body, or they may be constructed of a different material, such as a flexible or elastic strip, tape, or film. Interconnection of multiple patch sections in this manner allows the subject to affix one section to a first portion of the orbital margin 30 by sectional attachment means (e.g., a bioadhesive gel in contact with a sectional undersurface 18' of each section, allowing for removable attachment of the sections individually to their respective facial skin areas for application) and then affix a second section to a second portion of the orbital margin in an easy and positionally flexible manner. More specifically, the attachment of the first section does not strictly constrain positioning and attachment of the second section, because the interconnecting member joining the first and second sections can be manually deformed and/or stretched to provide for positional flexibility in placing and affixing the second section, and so on for each successive section to be attached. In this manner, attachment of the sectional patch is facilitated, and the patch is rendered more broadly applicable to different subjects having a range of anatomical dimensions of their orbital skin areas. In addition, flexibility of the interconnecting member(s) enhances comfort of the patch by easing potential stress that might otherwise be applied on the treated skin areas by a less flexible integration of the patch sections. Nonetheless, when a unitary patch body is provided with sectional members as described above, the anatomical configuration and inherent flexibility of the patch body provides for a suitable ease of anatomically direct attachment of the sections without excessive discomfort.

As exemplified in Fig. 4, one illustrative sectional orbital patch of the invention comprises multiple drug delivery sections of the body selected from a supraorbital drug delivery section 62 an infraorbital drug delivery section 64, a lateral drug delivery section 66, and/or a medial drug delivery section 68. These distinct sections may

be formed of a separate layer and/or distinct material from the primary patch body 14, or they may be integrally formed as individually contoured portions of a unitary patch body. The individual sections typically extend from the undersurface 18 of the patch body as contoured ridges or protrusions, as shown in Fig. 5. In this example, the patch features anatomically contoured ridges or protrusions comprising a supraorbital drug delivery section 62 an infraorbital drug delivery section 64, a lateral drug delivery section 66, and a medial drug delivery section 68. The contoured ridges or protrusions provide a comfortable, anatomically contoured shape to the patch, for example so that the undersurface of the patch body in a central portion 70 of the body is raised away from the orbital marginal skin surface(s) and does not impinge forcefully against the eye 32 of the wearer. In addition, the contoured ridges or protrusions typically serve an additional purpose of providing discrete drug delivery sections or reservoirs on, or within, the patch body that are adapted for effective, site-specific delivery of the anti-aging compound to one or more designated portions of the orbital margin 30--leaving sensitive areas such as the eyeball and conjunctiva relatively free of excessive exposure to the medication. In relation to these and other embodiments, the medication may be applied to the undersurfaces 18' of the drug delivery sections or infused or otherwise invested the material comprising the sections, or throughout the entire patch or mask body. In related aspects, the orbital patches and masks of the invention are constructed to ensure that the anti-aging effective compound is delivered to selected portions of the orbital margin to be treated while avoiding exposure of the mucus membranes of the eye and other sensitive tissues to the compound and other potentially irritating carriers and materials formulated therewith.

In other detailed embodiments of the invention a forehead patch 72 or mask 72' is provided that anatomically conforms to, and provides for treatment or prevention of skin aging in, all or part of a forehead skin area 74, and optionally in the case of a mask to one or more adjoining skin area(s), of a mammalian subject (see, e.g., Fig. 1). The forehead patch or mask also comprises a flexible patch or mask body 14 formed of a porous material sized and dimensioned to conform to a forehead skin surface or portion thereof of the subject. An attachment means is connected to the forehead patch or mask body for securely attaching the patch covering all or part of the forehead of the subject. An anti-aging effective compound is applied to, invested in, or otherwise provided in contact with an undersurface of the forehead patch or mask body. The undersurface of the

forehead patch or mask is similarly adapted for effective delivery of the anti-aging compound to a forehead skin surface for a period of time effective to alleviate symptoms of forehead skin aging. As described above for orbital patches 24 and masks 26, various portions of the forehead skin can be covered and treated by a forehead patch or mask, and the forehead patch or mask can be similarly constructed as a unitary patch or mask or to comprise multiple forehead patch or mask sections collectively arrayed and interconnected and adapted for drug delivery to multiple portions of the forehead skin and/or of other facial skin area(s). Thus, the forehead patch or mask can comprise a unitary body or a plurality of sections that individually or collectively cover any one or more portions of the forehead skin. Optionally, a forehead patch or mask 72' can be provided that conforms to all or part of the forehead skin and to one or more adjoining skin areas, such as the temporal 114 lateral facial skin area (see, e.g., Fig. 3).

In additional detailed embodiments of the invention a nasal patch 80 or mask 80' is provided for treatment or prevention of nasal skin aging in a mammalian subject (see, e.g., Fig. 1). The nasal patch or mask anatomically conforms to, and provides for treatment or prevention of skin aging in, all or part of the nasal skin, and optionally in the case of a mask to one or more adjoining skin area(s). The nasal patch or mask similarly comprises a flexible patch or mask body 14 formed of a porous material sized and dimensioned to conform to a nasal skin surface or portion thereof (e.g., a lateral nasal margin 82) of the subject. An attachment means is connected to the nasal patch or mask body for securely attaching the patch covering the nose or in contact with a nasal margin of the subject. An anti-aging effective compound is applied to, invested in, or otherwise provided in contact with an undersurface of the nasal patch or mask body. The undersurface of the nasal patch or mask is similarly adapted for effective delivery of the anti-aging compound to a nasal skin surface for a period of time effective to alleviate symptoms of nasal skin aging. As described above for orbital patches 24 and masks 26, various portions of the nasal skin can be covered and treated by a nasal patch or mask, and the nasal patch or mask can be similarly constructed as a unitary patch or mask or to comprise multiple nasal patch or mask sections collectively arrayed and interconnected and adapted for drug delivery to multiple portions of the nasal skin and/or of other facial skin area(s). Thus, for example, as shown in Fig. 1, the nasal patch or mask can comprise a unitary body or a plurality of sections that individually or collectively cover any one or more portions of the nasal skin selected from skin covering the root 84 of the nose, the

dorsum 86 of the nose, the ala 88 of the nose, and/or the lateral margins 82 of the nose. Optionally, the nasal patch or mask can additionally conform to an adjacent skin area such as one or more portion(s) of the orbital margin 30, or a skin area extending laterally from the ala of the nose between the cheek prominences of the face (e.g., as depicted for a nasal mask 80' in Fig. 1).

In other embodiments, the invention provides a labial patch 90 or mask for treatment or prevention of perilabial skin aging in a mammalian subject. The labial patch or mask anatomically conforms to, and provides for treatment or prevention of skin aging in, all or part of the perilabial skin, and optionally in the case of a mask to one or more adjoining skin area(s). The labial or mask patch comprises a flexible patch or mask body 14 formed of a porous material sized and dimensioned to conform to a labial margin of the subject. An attachment means 16 is connected to the patch or mask body for securely attaching the patch or mask in contact with the labial margin of the subject. An anti-aging effective compound is provided in contact with an undersurface 18 of the patch or mask body. The undersurface is adapted for effective delivery of the anti-aging compound to the labial margin for a period of time effective to alleviate symptoms of labial skin aging. The patch or mask can cover and treat all of the labial margin circumscribing the lips, or one or more selected portions of the labial margin, such as the upper labial margin 92, including the philtrum and philtral ridge (e.g., as provided by a supralabial patch 90 as shown in Fig. 1), or the lower labial margin (e.g., as provided by a sublabial patch conforming to a sublabial 94 area, or a lower facial mask 96 as shown in Fig. 1 covering combined sublabial and chin 98 areas of the facial skin). As described above for orbital patches 24 and masks 26, various portions of the perilabial skin can be covered and treated by a labial patch or mask, and the labial patch or mask can be similarly constructed as a unitary patch or mask or to comprise multiple labial patch or mask sections collectively arrayed and interconnected and adapted for drug delivery to multiple portions of the labial skin and/or of other facial skin area(s). Thus, for example, as shown in Fig. 4, the labial patch or mask can comprise a unitary body or a plurality of sections (e.g., supralabial 100 and sublabial 102 drug delivery sections) that individually or collectively conform to, and effectively deliver the anti-aging compound to, any one or more portions of the perilabial skin

In other embodiments, the invention provides a variety of lateral facial patches and masks 106 that substantially conform to, and effectively administer anti-aging

compounds to, all or part of one or more lateral facial skin areas, fore example lateral facial skin areas selected from a mandibular 110, maxillary 112, and/or temporal 114 lateral facial skin area. The mandibular facial skin area generally circumscribes the lower jaw. The maxillary facial skin area is between the upper and lower jaw and generally corresponds to the cheek area. The temporal facial skin area is between the upper jaw and hairline lateral to the orbital margin 30, and generally corresponds to the temple area. The various lateral facial patches and masks of the invention individually comprise a flexible patch or mask body 14 formed of a porous material sized and dimensioned to conform to a lateral facial skin area of the subject. An attachment means 16 is connected to the patch or mask body for securely attaching the patch or mask in contact with a lateral facial skin surface of the subject. An anti-aging effective compound is provided in contact with an undersurface 18 of the patch or mask body. The undersurface is adapted for effective delivery of the anti-aging compound to one or more lateral facial skin area(s) for a period of time effective to alleviate symptoms of lateral facial skin aging. The patch or mask can cover and treat all or part of one lateral facial skin, or all or part of multiple lateral facial skin areas. As described above for orbital patches 24 and masks 26, various portions of one or more lateral facial skin areas can be covered and treated by a lateral facial patch or mask. The lateral facial patch or mask can likewise be constructed as a unitary patch or mask or to comprise multiple lateral facial patch or mask sections collectively arrayed and interconnected and adapted for drug delivery to multiple portions of a single lateral facial skin area, of multiple facial skin areas, and/or of other facial skin area(s). Thus, as illustrated in Fig. 1, a lateral facial patch or mask 106 can comprise a unitary body or a plurality of sections that are collectively or individually sized and dimensioned to conform to one or more lateral facial skin areas selected from mandibular 110, maxillary 112, and/or temporal 114 lateral facial skin areas, and to effectively deliver the anti-aging compound thereto. For example, in the embodiment of the invention shown in Fig. 1, a lateral facial mask 106 is provided which comprises a tempero-maxillary-mandibular mask conforming to multiple lateral facial skin areas (covering all or portions of the temporal, maxillary, and mandibular facial skin areas) to treat or prevent skin aging in these areas.

In further detailed embodiments of the invention, facial masks 12 are provided that cover and deliver an anti-aging effective compound to a plurality of facial skin areas (see, e.g., Fig.s 1 and 3). Various configurations of facial masks are contemplated that anatomically conform to multiple facial skin areas. For example, masks

of the invention may conform to any two or more facial skin areas selected from: i) an orbital marginal area 30 (each (left and right) collectively including the supraorbital margin 36, infraorbital margin 46, lateral orbital margin 52, and medial orbital margin 58); ii) a nasal skin surface area (collectively including the nasal root 84, dorsum 86, ala 88 and lateral nasal margins 82); iii) a perilabial skin surface area (collectively including upper labial margin 92 and sublabial margin 94); iv) a forehead skin area 74; v) a chin skin area 98; vi) a madibular lateral facial skin area 110; vii) a maxillary lateral facial skin area 112; and viii) a temporal lateral facial skin area 114; and up to substantially the entire facial skin surface. As in the case of facial patches 10, the areas of facial skin to which the facial masks of the invention are directly attached (e.g., by adhesive contact with the skin) typically exclude sensitive tissues such as mucous membranes of the eyes, nose and mouth and are generally sized and dimensioned so as not to make adhesive contact with unshaven, hirsute facial skin areas such as the eyebrows. For example, this can be achieved by including cut-outs or openings 120 in the patch or mask that are sized and dimensioned to leave uncovered one or more sensitive or hirsute areas, for example the mouth, eyes, nares, eyebrows, and sideburns. Alternatively, the patch or mask may include specific attachment sections that form adhesive and chemical contacts with only selected portions of the facial skin and leave sensitive areas unaffected by adhesive materials and chemicals (including the anti-aging compound and any carriers and other potentially toxic or irritating agents formulated therewith). These specific attachment sections typically correspond to the discrete drug delivery sections of the patch or mask, as described above. For example, an orbital patch 24 or mask 26 may comprise specific, drug delivery and attachment sections selected from supraorbital 62, infraorbital 64, lateral orbital 66, and medial orbital 68 sections (Fig. 4). A labial patch 90 or mask can comprise specific, drug delivery and attachment sections selected from supralabial 100 and infralabial 102 sections. These sections will generally provide for anatomically conforming drug delivery contacts with the target skin can, and may also be modified (e.g., by coating each section with a biologically compatible adhesive such as a hydrogel) to provide sectional attachment means.

Exemplary facial masks 12 of the invention cover multiple facial skin areas in a manner that allows a reasonable range of movement between different muscular facial areas. For example, a lower facial mask 96 is depicted in Figure 1 that conforms to part of the mandibular 110 facial skin area, and further conforms to the chin 98 and sublabial 94

skin areas. This configuration of the facial mask provides for freedom of movement between the lower, mandibular and upper-medial maxillary portions of the face, as occurs during normal facial movements such as yawning and mastication. In another configuration, a lateral facial mask 106 is sized and dimensioned to conform to multiple lateral facial skin areas, for example to cover all or part of the mandibular 110, maxillary 112, and/or temporal 114 lateral facial skin areas (see, e.g., Fig. 1) to allow substantially unrestricted facial movements. In yet another embodiment, a facial mask is provided that conforms to both orbital margins to effectively deliver the anti-aging compound thereto, for example as provided by the orbital mask 26 depicted in Fig. 3, that optionally also covers one or more nasal skin area(s). A more discrete orbital mask is achieved by connecting two orbital patches 24 with a nasal bridging element 130 (e.g., an elastic connecting strip) (see, e.g., Fig.s 4 and 7).

As noted above, the facial masks 12 of the invention can be sized and dimensioned to cover and deliver an anti-aging effective compound to any selected plurality of facial skin areas. Thus, a mask of the invention may be shaped and sized to conform to any combination of the facial areas disclosed herein, including any combination of one or more: i) orbital marginal area(s) ii) nasal skin area; iii) perilabial skin surface area; iv) forehead skin area; v) chin skin area; vi) madibular lateral facial skin area; vii) maxillary lateral facial skin area; and viii) temporal lateral facial skin area. A specially configured mask to conform to or treat any combination of these areas can be constructed based on generally known facial anatomical characteristics in accordance with the teachings herein. Partial facial masks can cover any two, three, for or more discrete facial skin areas, for example a facial mask that conforms to all or portions of both orbital margins (see, e.g., Fig.s 3 and 4), to all or portions of both orbital margins and a nasal skin area (see, e.g., Fig. 3), to all or portions of the forehead and temporal skin areas (see, e.g., Fig. 3), to all or portions of the temporal, maxillary, and mandibular facial skin areas (see, e.g., Fig.s 1 and 3); or to perilabial and chin skin areas (see, e.g., Fig. 1). More extensive facial masks are also contemplated, such as a lower facial mask 140 (see, e.g., Fig 4) that conforms to three or more lower facial skin areas (e.g., to three or more of the perilabial, chin, mandibular, maxillary, and temporal skin areas). Full facial masks are also provided that substantially conform to all facial skin areas.

In yet additional embodiments of the invention, a neck skin patch or mask 146 is provided that is sized and dimensioned to conform to one or more skin surface area(s) of the neck, for example covering one or more sides 150 of the neck, throat skin area 152, back of neck skin area 154, and/or jowl skin area 156 of the neck under the chin 98 of the subject--and optionally to one or more of the facial skin areas described above (see, e.g., Fig.s 1 and 4). The neck patch or mask comprises a flexible patch or mask body 14 formed of a porous material. An attachment means 16 is connected to the patch or mask body for securely attaching the patch or mask in contact with the neck skin surface area(s). An anti-aging effective compound is provided in contact with an undersurface of the patch or mask body. The undersurface is adapted for effective delivery of the anti-aging compound to the skin area(s) of the neck for a period of time effective to alleviate symptoms of neck skin aging. Neck skin patches of the invention cover all or part of a specific neck skin surface area (e.g., all or part of the jowl, or throat, area). Neck skin masks of the invention cover a plurality of specific neck skin surface area(s) (e.g., all or part of the jowl and throat, or of the jowl, throat and sides of the neck, etc.), and up to the entire skin surface of the neck.

ANTI-AGING EFFECTIVE COMPOUNDS

The anti-aging effective compounds of the instant invention may comprise a single compound or a mixture of compounds that are individually or collectively effective to treat or prevent one or more symptoms of facial aging when the compound or mixture is delivered by a facial patch 10 or mask 12 applied for an effective period to effectuate delivery and action of the anti-aging compound(s) to a facial skin area. In alternative embodiments, multiple anti-aging effective compounds are coordinately delivered to the facial skin area, wherein at least one of the anti-aging effective compounds is administered by application of the patch or mask (e.g., with the compound(s) applied to the patch or mask undersurface or invested in the patch body 14), and a second or multiple additional anti-aging effective compounds is/are co-administered before or after patch application (e.g., by topical application before or after the patch or mask is applied). Thus, in certain embodiments, a first anti-aging compound is administered to the facial skin area to be treated by topical application, for example of an anti-aging compound formulated in a paste, cream or gel. Subsequently, a second anti-aging compound is administered that is

applied to the undersurface of a patch or mask or invested in the body of the patch or mask. In related embodiments, a first anti-aging compound is administered to the facial skin area to be treated via application of a patch or mask, and a second anti-aging compound is administered after removal of the patch or mask to the same facial skin area by topical application.

Anti-aging compounds that are useful within the methods and devices of the invention include a range of compounds that possess antioxidant activity. Multiple antioxidants and other known anti-aging compounds may be employed within the invention to provide additive or synergistic anti-aging results, yielding enhanced therapeutic and/or age-preventative effects. Antioxidant compounds that can be applied with the patches 10 and masks 12 of the invention, or coordinately administered therewith, include, but are not limited to, various non-enzymatic antioxidants such as vitamins (for example, vitamin A (retinol palmitate), B_6, C, D, D3 (cholecalciferol), and E (tocopherol acetate). Also useful are flavones, flavonoids, imidazoles, melatonin, alpha-hydroxycarboxylic acids (for example malic acid, glycolic acid, gluconic acid, salicylic acid and derivatives thereof), ubiquinones (e.g., CoQ10-CoQ15), glutathione, alpha-lipoic acid/DHLA, amino acids, proanthocyanadins, and various enzyme antioxidants such as glutathione peroxidase, catalase and superoxide dismutase. Any one or more of these anti-aging effective compounds can be administered simultaneously or coordinately with application of a patch or mask of the invention, optionally formulated in a carrier or delivery vehicle in a weight percentage of the active compound in the formulation ranging from: 0.01 to 50%; 0.05 to 25%; 0.1 to 10%; 0.5 to 5%; or approximately 0.3%.

Within certain embodiments of the invention, one or more anti-aging effective ubiquinones or plastiquinones are applied with the patch 10 or mask 12 of the invention to alleviate one or more symptoms of facial or neck skin aging. Also useful within these methods and devices are pharmaceutically acceptable, active salts and derivatives of ubiquinones and plastoquinones.

Ubiquinones function as electron transfer agents in biological, mitochondrial oxidation and thus play an important role in the energy metabolism of animal cells. Plastoquinones are analogous compounds from the plant kingdom that play a role in photosynthesis in the chloroplasts of plant cells. Plastoquinones differ from ubiquinones in three substituents on the quinone ring, wherein two methoxy groups in the

ubiquinones are replaced by methyl groups and one methyl group is replaced by a hydrogen atom in corresponding plastoquinone structures.

Ubiquinones have been reported as antioxidants that protect oxidation-sensitive substances against degradation induced by oxygen free radicals. These compounds, (also referred to as coenzymes Q_n) include a group of substances that have n isoprene units bonded in the form of a chain on their quinone ring (Q_0-Q_{10}). The number of isoprene units in the side chain of ubiquinones is designated by n variable in the common nomenclature term "coenzymes Q-n", wherein n is an integer. Among the useful ubiquinones for treating facial and neck skin aging within the methods and devices of the invention are ubiquinones or coenzymes Q-n, wherein n = from 0-12. The invention thus contemplates use of the quinone parent substance of ubiquinone without isoprene substituents. Often the selected anti-aging effective compound(s) comprise(s) one or more ubiquinones wherein n = from 1-12, and commonly wherein n = from 6 to 10. A sizable genus of useful ubiquinones are available for use within the invention and known in the art, as disclosed for example in "Rompp Chemie Lexikon" [Rompp's Chemical Dictionary], Georg Thieme Verlag Stuttgart, New York, 9th Edition, pages 4784-4785, and in The Merck Index, 11th Edition, Merck & Co., Inc. Rahway, N.Y., USA, Abstr. 9751 (1989) (each incorporated herein by reference). Exemplary ubiquinones for use within the invention include coenzyme Q-6, Q-9 or Q-10. Other examples of useful ubiquinones or derivatives thereof are alkylubicuinones, in particular 6-alkylubiquinones with preferably C_1-C_{12} -alkyl radicals. Within certain exemplary embodiments of the invention one or more decylubiquinone(s), for example 6-decylubiquinone, or 2,3-dimethoxy-5-methyl-6-decyl-1,4-benzoquinone, is/are selected as the anti-aging effective compound(s).

The plastoquinones are closely related to the ubiquinones in structure and are similarly referred to as isoprenoid quinines. They likewise carry a side chain of isoprene units on the quinone ring (see, e.g., "Rompp Chemie Lexikon" [Rompp's Chemical Dictionary], Georg Thieme Verlag, Stuttgart, New York, 9th Edition, page 3477, incorporated herein by reference). Plastoquinones for use within the invention will typically possess from 0-12, often from 1-10, and commonly from 6 to 10, isoprene units in the side chain. Further examples of plastoquinones according to the invention or derivatives thereof are alkyl-plastoquinones with preferably C_1-C_{12} -alkyl radicals. Within

certain exemplary embodiments of the invention one or more decylplastoquinone(s), for example 5- or 6-decylplastoquinone, or 2,3-dimethyl-5-decyl-1,4-benzoquinone, is/are selected as the anti-aging effective compound(s).

Within more detailed embodiments of the invention, one or more uqiquinone(s) and/or plastoquinone(s) selected from coenzyme Q-10, coenzyme Q-9, coenzyme Q-8, coenzyme Q-7, coenzyme Q-6, PQ-10 (i.e., plastoquinone with 10 isoprene units), PQ-9, PQ-8, PQ-7, and/or PQ-6 is/are selected as the anti-aging effective compound(s). The one or more ubiquinones or plastoquinones thus selected (e.g., coenzyme Q-10) is/are applied to, or otherwise invested in or provided in contact with, at least the undersurface 18 of the patch or mask body 14 for effective, controlled delivery of the active agent(s) to a facial or neck skin area. Alternatively, one or more ubiquinone(s) and/or plastoquinone(s) may be coordinately topically applied before or after application of a first anti-aging effective compound applied by a facial or neck patch 10 or mask 12 of the invention.

In more detailed aspects, the anti-aging compound delivered by the facial patch 10 or mask 12 or neck patch or mask 146 of the invention is effective, alone or in combination with additional, co-formulated or coordinately administered, anti-aging compound(s) and/or other biologically active skin treatment agent(s), for prophylaxis and/or treatment of one or more symptoms of facial skin aging (e.g., photoaging or actinic aging, and chronological aging). Each of the facial and neck patches and masks of the invention operates to deliver an effective amount of one or more anti-aging compound(s) over an effective time period of application of the patch or mask to substantially reduce or prevent one or more symptoms of facial and/or neck skin aging in the facial and/or neck skin area(s) to which the patch or mask is applied, wherein exemplary symptoms are selected from:

a) Degeneration of the microvascular system;

b) Flaccidity and development of wrinkles due to a decrease in and/or crosslinking of collagen, accumulation of glucosaminoglycans (base substance) and/or solar elastosis (elastin clumping);

c) Flattening of the retial cones, associated with a reduction in thickness or area

between the dermis and epidermis through which substances are exchanged for healthy metabolism of the epidermis;

d) Restricted regenerative turnover in the epidermis associated with defective hornification, leading to drying out of the skin, roughness of the skin, chapping of the skin and/or flaking;

e) Defective regulation of cell division (proliferation) and cell maturation (differentiation) in the epidermis associated with cellular atypia, atrophies, and loss of polarity; and/or

f) Local hyper- and hypopigmentation and/or abnormal pigmentation (age spots).

For example, following single or repeated application(s) of a facial patch 10 or mask 12 of the invention, substantial reduction or prevention of facial skin aging is achieved as marked by at least a 20% reduction, more typically a 30% reduction, often a 40-50% reduction, and as much as a 75%, 85%, 90%, 95%, or greater, reduction in one or more of the foregoing symptoms of facial skin aging. To demonstrate this efficacy, various morphologic and/or physiologic indices associated with the foregoing aging symptoms are routinely measured in suitable test and control subjects in accordance with known procedures for assaying the efficacy of anti-aging methods and formulations. A measureable reduction of these indices correlated with aging in test subject skin areas to which a facial patch or mask of the invention is applied (e.g., as compared to values measured for control subjects in which a placebo patch or mask lacking the anti-aging effective compound is applied) will demonstrate the substantial reduction or prevention of the facial skin aging symtom(s) as defined above. This unprecedented efficacy can be demonstrated by a range of known morphological assays and physiological assays for measuring, in comparable test and control subjects, such skin aging characteristics as:

a) Morphological and/or physiological indices correlating with degeneration of the microvascular system;

b) Morphological and/or physiological indices correlating with flaccidity and development of wrinkles (including, but not limited to, crosslinking of collagen,

accumulation of glucosaminoglycans, and/or elastin clumping);

c) Morphological and/or physiological indices correlating with flattening of the retial cones (including, but not limited to, reduction in thickness or area between the dermis and epidermis);

d) Morphological and/or physiological indices correlating with restricted regenerative turnover in the epidermis (including, but not limited to, drying out of the skin, roughness of the skin, chapping of the skin and/or flaking);

e) Morphological and/or physiological indices correlating with defective regulation of cell division and/or maturation in the epidermis (including, but not limited to, cellular atypia, atrophies, and loss of polarity); and/or

f) Morphological and/or physiological indices correlating with local hyper- and hypopigmentation and/or abnormal pigmentation of the subject skin area(s).

Numerous suitable assays are contemplated for measuring these indices and demonstrating the efficacy of the facial patches 10 and masks 12 and neck skin patches and masks 146 of the invention. Suitable assays are well known and routinely practiced in the art, as supplemented by the teachings herein. With the application of these combined teachings, it can be readily demonstrated that a single or repeat application of a facial or neck patch or mask of the invention substantially reduces or prevents one or more of the foregoing morphological and/or physiological indices correlating with corresponding symptom(s) of facial and/or neck skin aging at least 20%, more typically at least 30%, often at least 40-50%, and as much as a 75%, 85%, 90%, 95%, or greater, compared with the corresponding value of the same morphological and/or physiological indices measured in an acceptable control model or system. Often, achievement of these desired results requires prolonged application of the patch or mask of the invention, for at least a single application period of 2-4 hours, more typically at least 4 hours, often for 4-8 hours, and commonly for at least 8 hours.

To render the patch or mask functional for continued delivery of the anti-aging effective compound for these prolonged therapy periods, the anti-aging compound is

formulated, and/or the patch or mask body is constructed, so as to facilitate controlled, prolonged release of the anti-aging effective compound for an effective delivery period of 2-4 hours, more typically at least 4 hours, often for 4-8 hours, and commonly for at least 8 hours. Many of the patches and masks provided herein are operable for prolonged delivery of an overnight formulation of an anti-aging effective compound, thereby achieving prolonged delivery of the active agent with continuous anti-aging efficacy for periods of 7 hours or more, up to 12 hours and even all day (16-24 hours), without unacceptable adverse side effects such as excessive skin irritation, dehydration, occlusion hydration (pruning), and the like.

This prolonged, controlled release capacity of the facial and neck patches and masks of the invention can be routinely demonstrated by known in vitro and in vivo assays, for example assays as described below that measure skin concentration and residence time for an anti-aging compound. In certain embodiments, continued or "time-release" delivery is achieved at a substantially consistent rate of delivery for the duration of the time release period for which the patch or mask is applied to the skin, wherein the concentration of the anti-aging compound(s) at the skin surface remains substantially equivalent at an initial time point (e.g., one-half hour) after application of the patch or mask and at subsequent time points (e.g., 2, 4, 6, 8 hours). However, in other embodiments the rate of delivery declines after an initial time point, but the patch or mask still delivers an anti-aging effective concentration of the anti-aging compound(s) throughout the duration of the specified time-release period.

POLYMERIC DELIVERY VEHICLES AND METHODS

Within certain aspects of the invention, the anti-aging effective compound(s), and, optionally, other biologically active agent(s) and/or delivery-enhancing agents as described herein, are incorporated within a biologically compatible carrier or delivery vehicle, such as a polymeric carrier or delivery vehicle. In exemplary embodiments, the carrier delivery vehicle comprises a polymer that is non-toxic and non-irritating to the skin following prolonged exposure thereto and is otherwise biologically compatible for the uses disclosed herein. The polymeric carrier or delivery vehicle functions as a carrier or base for the anti-aging effective compound(s) and facilitates

loading or containment of the anti-aging compound onto the patch 10 or mask 12 undersurface 18 or within all or a portion of the porous patch or mask body 14. In addition, the delivery vehicle will optionally serve as a controlled delivery vehicle to facilitate time-release delivery of the anti-aging compound(s) to the facial or neck skin area(s) to be treated.

Useful polymeric carriers within the methods and devices of the invention include polymeric powders, gels, pastes, matrices and microparticulate delivery vehicles, among other polymer forms. The polymer can be of plant, animal, or synthetic origin. Often the polymer is crosslinked. Additionally, in these polymeric delivery systems the anti-aging effective compound(s) can be functionalized in a manner where it can be covalently bound to the polymer for enhanced loading, retention, stability delivery and/or bioavailability of the active compound(s). In other embodiments, the polymer is chemically modified with an inhibitor of enzymes or other agents that may degrade or inactivate the anti-aging effective compound(s) or other biologically active or delivery enhancing agent(s). In certain formulations, the polymer is a partially or completely water insoluble but water swellable polymer, e.g, a hydrogel. Polymers useful in this aspect of the invention are desirably water interactive and/or hydrophilic in nature to absorb significant quantities of water, and they often form hydrogels when placed in contact with water or aqueous media for a period of time sufficient to reach equilibrium with water. In more detailed embodiments, the polymer is a hydrogel which, when placed in contact with excess water, absorbs at least two times its weight of water at equilibrium when exposed to water at room temperature (see, e.g., U.S. Patent No. 6,004,583, incorporated herein by reference).

Drug delivery systems based on biodegradable polymers are particularly useful within the methods and devices of the invention because such systems are typically broken down either by hydrolysis or by enzymatic reaction into non-toxic molecules. These delivery vehicles can therefore be employed effectively in conjunction with a facial or neck patch or mask of the invention for long-term release of anti-aging effective compounds. The rate of degradation of biodegradable polymers in this regard can be controlled by manipulating the composition of the biodegradable polymer matrix. Exemplary biodegradable polymers for use within the invention include, but are not limited to, poly(glycolic acid) (PGA), poly-(lactic acid) (PLA), and poly(D,L-lactic-co-

glycolic acid) (PLGA), each of which produces degradation products having low toxicity and excellent biocompatibility (Mehta et al, J. Control. Rel.29:375-384, 1994, incorporated herein by reference).

For prolonging the biological activity of anti-aging effective compounds and other biologically active and delivery-enhancing agents within the invention, the subject compounds and agents may be incorporated into a polymeric matrix, e.g., a polyorthoester, polyanhydride, or polyester matrix, to yield sustained activity and release of the subject compounds and agents (e.g., as determined by the degradation of the polymer matrix). Exemplary polymeric matrices are described and characterized in, e.g., Heller, Formulation and Delivery of Proteins and Peptides, pp. 292-305, Cleland et al., Eds., ACS Symposium Series 567, Washington DC, 1994; Tabata et al., Pharm. Res.10:487-496, 1993; and Cohen et al., Pharm. Res.8:713-720, 1991 (each incorporated herein by reference). Useful polymeric matrices for carrying and delivering anti-aging effective compounds may be applied to, or incorporated within, the patch 10 or mask 12 body 14 during or after construction of the patch or mask body, and they may in other embodiments form a primary or sole constituent of the patch or mask body.

In additional aspects of the invention, polymeric carriers and delivery vehicles are provided for use within the invention that include derivatives and chemically or physically modified versions of the foregoing types of polymers, in addition to other naturally occurring or synthetic polymers, gums, resins, and other agents. Also contemplated for use within the invention are blends of these materials with each other, and with other polymers, so long as the alterations, modifications or blending do not adversely affect the desired properties, such as water absorption, hydrogel formation, and/or chemical stability for useful application. In more detailed aspects of the invention, polymers such as nylon, acrylan and other normally hydrophobic synthetic polymers may be modified by reaction to gain an additional useful function of water swellability and/or an ability to form stable gels in aqueous media.

Suitable polymers for use within the invention should generally be stable alone and in combination with the selected anti-aging effective compound(s) (e.g., Coenzyme Q10) and optional additional biologically active agent(s) and/or delivery-enhancing agent(s). Often, the polymers will form stable hydrogels in a range of pH conditions from about pH 1 to about pH 10. More typically, they are stable and form

polymers under pH conditions ranging from about 3 to 9, without additional protective coatings. However, desired stability properties may be adapted to physiological parameters characteristic of the targeted site of delivery (e.g., a surface or basal layer of the facial or neck epidermis). Therefore, in certain formulations higher or lower stabilities at a particular pH and in a selected chemical or biological environment will be more desirable.

Within additional embodiments of the invention, the anti-aging effective compound(s) is/are formulated with one or more absorption-promoting polymers that enhance absorption of the anti-aging compound(s) from the patch undersurface 18 or body 14 into or across the facial or neck skin (e.g., to the basal cell layer of the facial epidermis). These absorption-promoting polymers may include any polymer that enhances facial skin absorption, for example homo- and copolymers based on various combinations of the following vinyl monomers: acrylic and methacrylic acids, acrylamide, methacrylamide, hydroxyethylacrylate or methacrylate, vinylpyrrolidones, as well as polyvinylalcohol and its co- and terpolymers, polyvinylacetate, its co- and terpolymers with the above listed monomers and 2-acrylamido-2-methyl-propanesulfonic acid (AMPS®). Particularly useful are copolymers of the above listed monomers with copolymerizable functional monomers such as acryl or methacryl amide acrylate or methacrylate esters where the ester groups are derived from straight or branched chain alkyl, aryl having up to four aromatic rings which may contain alkyl substituents of 1 to 6 carbons; steroidal, sulfates, phosphates or cationic monomers such as N,N-dimethylaminoalkyl(meth)acrylamide, dimethylaminoalkyl(meth)acrylate, (meth)acryloxyalkyltrimethylammonium chloride, (meth)acryloxyalkyldimethylbenzyl ammonium chloride.

Additional absorption-promoting polymers for use within the invention are those classified as dextrans, dextrins, and from the class of materials classified as natural gums and resins, or from the class of natural polymers such as processed collagen, chitin, chitosan, pullalan, zooglan, alginates and modified alginates such as "Kelcoloid" (a polypropylene glycol modified alginate) gellan gums such as "Kelocogel", Xanathan gums such as "Keltrol", estastin, alpha hydroxy butyrate and its copolymers, hyaluronic acid and its derivatives, polylactic and glycolic acids.

Yet another useful class of polymers applicable within the instant invention are olefinically-unsaturated carboxylic acids containing at least one activated carbon-to-carbon olefinic double bond, and at least one carboxyl group; that is, an acid or functional

group readily converted to an acid containing an olefinic double bond which readily functions in polymerization because of its presence in the monomer molecule, either in the alpha-beta position with respect to a carboxyl group, or as part of a terminal methylene grouping. Olefinically-unsaturated acids of this class include such materials as the acrylic acids typified by acrylic acid itself, alpha-cyano acrylic acid, beta methylacrylic acid (crotonic acid), alpha-phenyl acrylic acid, beta-acryloxy propionic acid, cinnamic acid, p-chloro cinnamic acid, 1-carboxy-4-phenyl butadiene-1,3, itaconic acid, citraconic acid, mesaconic acid, glutaconic acid, aconitic acid, maleic acid, fumaric acid, and tricarboxy ethylene. As used herein, the term "carboxylic acid" includes the polycarboxylic acids and those acid anhydrides, such as maleic anhydride, wherein the anhydride group is formed by the elimination of one molecule of water from two carboxyl groups located on the same carboxylic acid molecule.

Representative acrylates useful as delivery vehicles and/or absorption-promoting agents within the invention include methyl acrylate, ethyl acrylate, propyl acrylate, isopropyl acrylate, butyl acrylate, isobutyl acrylate, methyl methacrylate, methyl ethacrylate, ethyl methacrylate, octyl acrylate, heptyl acrylate, octyl methacrylate, isopropyl methacrylate, 2-ethylhexyl methacrylate, nonyl acrylate, hexyl acrylate, n-hexyl methacrylate, and the like. Higher alkyl acrylic esters are decyl acrylate, isodecyl methacrylate, lauryl acrylate, stearyl acrylate, behenyl acrylate and melissyl acrylate and methacrylate versions thereof. Mixtures of two or three or more long chain acrylic esters may be successfully polymerized with one of the carboxylic monomers. Other comonomers include olefins, including alpha olefins, vinyl ethers, vinyl esters, and mixtures thereof.

Other vinylidene monomers may also be used as delivery vehicles and/or absorption-promoting agents within the methods and compositions of the invention, including the acrylic nitriles. Useful alpha, beta-olefinically unsaturated nitriles are preferably monoolefinically unsaturated nitriles having from 3 to 10 carbon atoms such as acrylonitrile, methacrylonitrile, and the like. Most preferred are acrylonitrile and methacrylonitrile. Acrylic amides containing from 3 to 35 carbon atoms including monoolefinically unsaturated amides also may be used. Representative amides include acrylamide, methacrylamide, N-t-butyl acrylamide, N-cyclohexyl acrylamide, higher alkyl amides, where the alkyl group on the nitrogen contains from 8 to 32 carbon atoms, acrylic

amides including N-alkylol amides of alpha, beta-olefinically unsaturated carboxylic acids including those having from 4 to 10 carbon atoms such as N-methylol acrylamide, N-propanol acrylamide, N-methylol methacrylamide, N-methylol maleimide, N-methylol maleamic acid esters, N-methylol-p-vinyl benzamide, and the like.

Yet additional useful delivery vehicles and/or absorption-promoting materials are alpha-olefins containing from 2 to 18 carbon atoms, more preferably from 2 to 8 carbon atoms; dienes containing from 4 to 10 carbon atoms; vinyl esters and allyl esters such as vinyl acetate; vinyl aromatics such as styrene, methyl styrene and chloro-styrene; vinyl and allyl ethers and ketones such as vinyl methyl ether and methyl vinyl ketone; chloroacrylates; cyanoalkyl acrylates such as alpha-cyanomethyl acrylate, and the alpha-, beta-, and gamma-cyanopropyl acrylates; alkoxyacrylates such as methoxy ethyl acrylate; haloacrylates as chloroethyl acrylate; vinyl halides and vinyl chloride, vinylidene chloride and the like; divinyls, diacrylates and other polyfunctional monomers such as divinyl ether, diethylene glycol diacrylate, ethylene glycol dimethacrylate, methylene-bis-acrylamide, allylpentaerythritol, and the like; and bis (beta-haloalkyl) alkenyl phosphonates such as bis(beta-chloroethyl) vinyl phosphonate and the like as are known to those skilled in the art. Copolymers wherein the carboxy containing monomer is a minor constituent, and the other vinylidene monomers present as major components are readily prepared in accordance with the teachings known in the art and further described herein.

In more detailed aspects of the invention, topical delivery of the anti-aging effective compound is enhanced by retaining the anti-aging effective compound(s) (e.g., Coenzyme Q10) and, optionally, other biologically active and/or delivery enhancing agents, in a slow-release or enzymatically or physiologically protective carrier or vehicle, for example a hydrogel that shields the active agent from the action of the degradative enzymes. In certain embodiments, the anti-aging effective compound is bound by chemical means to the carrier or vehicle, to which may also be admixed or bound additional agents such as enzyme inhibitors, etc. The anti-aging effective compound may alternately be immobilized through sufficient physical entrapment within the carrier or vehicle, e.g., a polymer matrix.

When hydrogels are employed as delivery vehicles and/or absorption promoting agents within the invention, these may be composed of synthetic copolymers from the group of acrylic and methacrylic acids, acrylamide, methacrylamide,

hydroxyethylacrylate (HEA) or methacrylate (HEMA), and vinylpyrrolidones which are water interactive and swellable. Specific illustrative examples of useful polymers, for the delivery of anti-aging effective compounds are the following types of polymers: (meth)acrylamide and 0.1 to 99 wt. % (meth)acrylic acid; (meth)acrylamides and 0.1-75 wt % (meth)acryloxyethyl trimethyammonium chloride; (meth)acrylamide and 0.1-75 wt % (meth)acrylamide; acrylic acid and 0.1-75 wt % alkyl(meth)acrylates; (meth)acrylamide and 0.1-75 wt % AMPS® (trademark of Lubrizol Corp.); (meth)acrylamide and 0 to 30 wt % alkyl(meth)acrylamides and 0.1-75 wt % AMPS® ; (meth)acrylamide and 0.1-99 wt. % HEMA; (metb)acrylamide and 0.1 to 75 wt % HEMA and 0.1 to 99%(meth)acrylic acid; (meth)acrylic acid and 0.1-99 wt % HEMA; 50 mole % vinyl ether and 50 mole % maleic anhydride; (meth)acrylamide and 0.1 to 75 wt % (meth)acryloxyalky dimethyl benzylammonium chloride; (meth)acrylamide and 0.1 to 99 wt % vinyl pyrrolidone; (meth)acrylamide and 50 wt % vinyl pyrrolidone and 0.1-99.9 wt % (meth)acrylic acid; (meth)acrylic acid and 0.1 to 75 wt % AMPS® and 0.1-75 wt % alkyl(meth)acrylamide. In the above examples, alkyl means C_1 to C_{30}, preferably C_1 to C_{22}, linear and branched and C_4 to C_{16} cyclic; where (meth) is used, it means that the monomers with and without the methyl group are included. Other useful hydrogel polymers are swellable, but insoluble versions of poly(vinyl pyrrolidone) starch, carboxymethyl cellulose and polyvinyl alcohol.

Additional polymeric hydrogel materials for use within the invention include (poly) hydroxyalkyl (meth)acrylate: anionic and cationic hydrogels: poly(electrolyte) complexes; poly(vinyl alcohols) having a low acetate residual: a swellable mixture of crosslinked agar and crosslinked carboxymethyl cellulose: a swellable composition comprising methyl cellulose mixed with a sparingly crosslinked agar; a water swellable copolymer produced by a dispersion of finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, or isobutylene; a water swellable polymer of N-vinyl lactams; swellable sodium salts of carboxymethyl cellulose; and the like.

Other gelable, fluid imbibing and retaining polymers useful for forming the hydrophilic hydrogel for topical delivery of anti-aging effective compounds to facial and neck skin areas in conjunction with application of a facial or neck patch or mask of the invention include pectin; polysaccharides such as agar, acacia, karaya, tragacenth, algins

and guar and their crosslinked versions; acrylic acid polymers, copolymers and salt derivatives, polyacrylamides; water swellable indene maleic anhydride polymers; starch graft copolymers; acrylate type polymers and copolymers with water absorbability of about 2 to 400 times its original weight; diesters of polyglucan; a mixture of crosslinked poly(vinyl alcohol) and poly(N-vinyl-2-pyrrolidone); polyoxybutylene-polyethylene block copolymer gels; carob gum; polyester gels; poly urea gels; polyether gels; polyamide gels; polyimide gels; polypeptide gels; polyamino acid gels; poly cellulosic gels; crosslinked indene-maleic anhydride acrylate polymers; and polysaccharides.

Synthetic hydrogel polymers for use within the invention may be made by combining various monomers in selected ratios. The hydrogel can be crosslinked and generally possesses the ability to imbibe and absorb fluid and swell or expand to an enlarged equilibrium state. The hydrogel typically swells or expands after initial formulation (e.g., before or after application of the patch to the facial or neck skin surface), absorbing about 2-5, 5-10, 10-50, up to 50-100 or more times fold its weight of water. The optimum degree of swellability for a given hydrogel will be determined for different anti-aging effective compounds depending upon such factors as molecular weight, size, solubility and diffusion characteristics of the active agent carried by or entrapped or encapsulated within the polymer, and the specific spacing and cooperative chain motion associated with each individual polymer.

Certain hydrophilic polymers useful within the invention are water insoluble but water swellable. Such water swollen polymers are typically referred to as hydrogels or gels. Such gels may be conveniently produced from water soluble polymer by the process of crosslinking the polymers by a suitable crosslinking agent. However, stable hydrogels may also be formed from specific polymers under defined conditions of pH, temperature and/or ionic concentration, according to known methods in the art. Typically the polymers are cross-linked, that is, cross-linked to the extent that the polymers possess good hydrophilic properties, have improved physical integrity (as compared to non cross-linked polymers of the same or similar type) and exhibit improved ability to retain within the gel network the anti-aging effective compound of interest and optional additional compounds for coadministration therewith such as an enzyme inhibitor, while retaining the ability to release the active agent(s) at the appropriate location and time.

Generally hydrogel polymers for use within the invention are crosslinked with a difunctional cross-linking in the amount of from 0.01 to 25 weight percent, based on the weight of the monomers forming the copolymer, and more preferably from 0.1 to 20 weight percent and more often from 0. 1 to 15 weight percent of the crosslinking agent. Another useful amount of a crosslinking agent is 0.1 to 10 weight percent. Tri, tetra or higher multifunctional crosslinking agents may also be employed. When such reagents are utilized, lower amounts may be required to attain equivalent crosslinking density, i.e., the degree of crosslinking, or network properties that are sufficient to contain effectively the anti-aging effective compound(s). The crosslinks can be covalent, ionic or hydrogen bonds with the polymer possessing the ability to swell in the presence of water containing fluids. Such crosslinkers and crosslinking reactions are known to those skilled in the art and in many cases are dependent upon the polymer system. Thus a crosslinked network may be formed by free radical copolymerization of unsaturated monomers.

Polymeric hydrogels may also be formed by crosslinking preformed polymers by reacting functional groups found on the polymers such as alcohols, acids, amines with such groups as glyoxal, formaldehyde or glutaraldehyde, bis anhydrides and the like. The polymers also may be cross-linked with any polyene, e.g. decadiene or trivinyl cyclohexane; acrylamides, such as N,N-methylene-bis (acrylamide); polyfunctional acrylates, such as trimethylol propane triacrylate; or polyfunctional vinylidene monomer containing at least 2 terminal CH.sub.2 < groups, including, for example, divinyl benzene, divinyl naphthlene, allyl acrylates and the like. In certain embodiments, cross-linking monomers for use in preparing the copolymers are polyalkenyl polyethers having more than one alkenyl ether grouping per molecule, which may optionally possess alkenyl groups in which an olefinic double bond is present attached to a terminal methylene grouping (e.g., made by the etherification of a polyhydric alcohol containing at least 2 carbon atoms and at least 2 hydroxyl groups). Compounds of this class may be produced by reacting an alkenyl halide, such as allyl chloride or allyl bromide, with a strongly alkaline aqueous solution of one or more polyhydric alcohols. The product may be a complex mixture of polyethers with varying numbers of ether groups. Efficiency of the polyether cross-linking agent increases with the number of potentially polymerizable groups on the molecule. Typically, polyethers containing an average of two or more alkenyl ether groupings per molecule are used. Other useful cross-linking monomers include for example, diallyl esters, dimethallyl ethers, allyl or methallyl

acrylates and acrylamides, tetravinyl silane, polyalkenyl methanes, diacrylates, and dimethacrylates, divinyl compounds such as divinyl benzene, polyallyl phosphate, diallyloxy compounds and phosphite esters and the like. Typical agents are allyl pentaerythritol, allyl sucrose, trimethylolpropane triacrylate, 1,6-hexanediol diacrylate, trimethylolpropane diallyl ether, pentaerythritol triacrylate, tetramethylene dimethacrylate, ethylene diacrylate, ethylene dimethacrylate, triethylene glycol dimethacrylate, and the like. Allyl pentaerythritol, trimethylolpropane diallylether and allyl sucrose provide suitable polymers. When the cross-linking agent is present, the polymeric mixtures usually contain between about 0.01 to 20 weight percent, e.g., 1%, 5%, or 10% or more by weight of cross-linking monomer based on the total of carboxylic acid monomer, plus other monomers.

Polymers such as hydrogels useful within the invention may incorporate functional linked agents such as glycosides chemically incorporated into the polymer for enhancing topical bioavailability of anti-aging effective compounds and other biologically active agents formulated therewith. Examples of such glycosides are glucosides, fructosides, galactosides, arabinosides, mannosides and their alkyl substituted derivatives and natural glycosides such as arbutin, phlorizin, amygdalin, digitonin, saponin, and indican. There are several ways in which a typical glycoside may be bound to a polymer. For example, the hydrogen of the hydroxyl groups of a glycoside or other similar carbohydrate may be replaced by the alkyl group from a hydrogel polymer to form an ether. Also, the hydroxyl groups of the glycosides may be reacted to esterify the carboxyl groups of a polymeric hydrogel to form polymeric esters in situ. Another approach is to employ condensation of acetobromoglucose with cholest-5-en-3beta-ol on a copolymer of maleic acid. N-substituted polyacrylamides can be synthesized by the reaction of activated polymers with omega-aminoalkylglycosides: (1) (carbohydrate-spacer)(n)-polyacrylamide, `pseudopolysaccharides`; (2) (carbohydrate spacer)(n)-phosphatidylethanolamine(m)-polyacrylamide, neoglycolipids, derivatives of phosphatidylethanolamine; (3) (carbohydrate-spacer)(n)-biotin(m)-polyacrylamide. These biotinylated derivatives may attach to lectins on target cell surfaces to facilitate absorption of the anti-aging effective compound, e.g., a polymer encapsulated protein or peptide.

Within more detailed aspects of the invention, anti-aging effective compound (e.g., Coenzyme Q10), and, optionally, additional, secondary active agents such

as other antioxidant compounds, protease inhibitor(s), etc., are modified and bound to a polymeric carrier or matrix. For example, this may be accomplished by chemically binding a Coenzyme Q10 active agent and other optional agent(s) within a crosslinked polymer network. It is also possible to chemically modify the polymer separately with an interactive agent such as a glycosidal containing molecule. In certain aspects, the anti-aging effective compound(s) and optional secondary active agent(s), may be functionalized, i.e., wherein an appropriate reactive group is identified or is chemically added to the active agent(s). For example, an ethylenic polymerizable group may be added, and the functionalized active agent is then copolymerized with monomers and a crosslinking agent using a standard polymerization method such as solution polymerization (usually in water), emulsion, suspension or dispersion polymerization. Often, the functionalizing agent is provided with a high enough concentration of functional or polymerizable groups to insure that multiple sites on the active agent(s) are functionalized.

After functionalization, the functionalized active agent(s) is/are mixed with monomers and a crosslinking agent which comprise the reagents from which the polymer of interest is formed. Polymerization is then induced in this medium to create a polymer containing the bound active agent(s). The polymer is then washed with water or other appropriate solvents and otherwise purified to remove trace unreacted impurities and, if necessary, ground or broken up by physical means such as by stirring, forcing it through a mesh, ultrasonication or other suitable means to a desired particle size. The solvent, usually water, is then removed in such a manner as to not denature or otherwise degrade the active agent(s). One desired method is lyophilization (freeze drying) but other methods are available and may be used (e.g., vacuum drying, air drying, spray drying, etc.).

In additional aspects of the invention, the anti-aging effective compound (e.g., Coenzyme Q10) and optional additional anti-aging effective compounds and/or delivery-enhancing agents, including anti-aging effective compounds (e.g., anti-oxidant compounds), peptides, proteins, nucleosides, and other molecules which are bioactive *in vivo*, are conjugation-stabilized by covalently bonding one or more of the active or enhancing agent(s) to a polymer incorporating as an integral part thereof both a hydrophilic moiety, e.g., a linear polyalkylene glycol, and a lipophilic moiety (see, e.g.,

U.S. Patent No. 5,681,811, incorporated herein by reference). In one aspect, a anti-aging effective compound is covalently coupled with a polymer comprising (i) a linear polyalkylene glycol moiety and (ii) a lipophilic moiety, wherein the active agent, linear polyalkylene glycol moiety, and the lipophilic moiety are conformationally arranged in relation to one another such that the active therapeutic agent has an enhanced *in vivo* resistance to enzymatic degradation (i.e., relative to its stability under similar conditions in an unconjugated form devoid of the polymer coupled thereto). In another aspect, the conjugation-stabilized formulation has a three-dimensional conformation comprising the anti-aging effective compound covalently coupled with a polysorbate complex comprising (i) a linear polyalkylene glycol moiety and (ii) a lipophilic moiety, wherein the active agent, the linear polyalkylene glycol moiety and the lipophilic moiety are conformationally arranged in relation to one another such that (a) the lipophilic moiety is exteriorly available in the three-dimensional conformation, and (b) the active agent in the composition has an enhanced *in vivo* resistance to enzymatic degradation.

In a further related aspect of the invention, a multiligand conjugated complex is provided which comprises an anti-aging effective compound (e.g., Coenzyme Q10) and/or other biologically active or delivery-enhancing agent covalently coupled with a triglyceride backbone moiety through a polyalkylene glycol spacer group bonded at a carbon atom of the triglyceride backbone moiety, and at least one fatty acid moiety covalently attached either directly to a carbon atom of the triglyceride backbone moiety or covalently joined through a polyalkylene glycol spacer moiety (see, e.g., U.S. Patent No. 5,681,811, incorporated herein by reference). In such multiligand conjugated therapeutic agent complexes, the alpha' and beta carbon atoms of the triglyceride bioactive moiety may have fatty acid moieties attached by covalently bonding either directly thereto, or indirectly covalently bonded thereto through polyalkylene glycol spacer moieties. Alternatively, a fatty acid moiety may be covalently attached either directly or through a polyalkylene glycol spacer moiety to the alpha and alpha' carbons of the triglyceride backbone moiety, with the bioactive therapeutic agent being covalently coupled with the gamma-carbon of the triglyceride backbone moiety, either being directly covalently bonded thereto or indirectly bonded thereto through a polyalkylene spacer moiety. It will be recognized that a wide variety of structural, compositional, and conformational forms are possible for the multiligand conjugated therapeutic agent complex comprising the triglyceride backbone moiety, within the scope of the invention. It is further noted that in

such a multiligand conjugated therapeutic agent complex, the anti-aging effective compound(s) may advantageously be covalently coupled with the triglyceride modified backbone moiety through alkyl spacer groups, or alternatively other acceptable spacer groups, within the scope of the invention. As used in such context, acceptability of the spacer group refers to steric, compositional, and end use application specific acceptability characteristics.

In yet additional aspects of the invention, a conjugation-stabilized complex is provided which comprises a polysorbate complex comprising a polysorbate moiety including a triglyceride backbone having covalently coupled to alpha, alpha' and beta carbon atoms thereof functionalizing groups including (i) a fatty acid group; and (ii) a polyethylene glycol group having a anti-aging effective compound or moiety covalently bonded thereto, e.g., bonded to an appropriate functionality of the polyethylene glycol group (see, e.g., U.S. Patent No. 5,681,811, incorporated herein by reference). Such covalent bonding may be either direct, e.g., to a hydroxy terminal functionality of the polyethylene glycol group, or alternatively, the covalent bonding may be indirect, e.g., by reactively capping the hydroxy terminus of the polyethylene glycol group with a terminal carboxy functionality spacer group, so that the resulting capped polyethylene glycol group has a terminal carboxy functionality to which the anti-aging effective compound or other biologically active or delivery-enhancing agent or moiety may be covalently bonded.

In yet additional aspects of the invention, a stable, aqueously soluble, conjugation-stabilized complex is provided which comprises an anti-aging effective compound (e.g., Coenzyme Q10) and/or other biologically active or delivery-enhancing agent covalently coupled to a physiologically compatible polyethylene glycol (PEG) modified glycolipid moiety. In such complex, the anti-aging effective compound may be covalently coupled to the physiologically compatible PEG modified glycolipid moiety by a labile covalent bond at a free amino acid group of the active agent, wherein the labile covalent bond is scissionable *in vivo* by biochemical hydrolysis and/or proteolysis. The physiologically compatible PEG modified glycolipid moiety may advantageously comprise a polysorbate polymer, e.g., a polysorbate polymer comprising fatty acid ester groups selected from the group consisting of monopalmitate, dipalmitate, monolaurate, dilaurate, trilaurate, monoleate, dioleate, trioleate, monostearate, distearate, and tristearate. In such complex, the physiologically compatible PEG modified glycolipid moiety may

suitably comprise a polymer selected from the group consisting of polyethylene glycol ethers of fatty acids, and polyethylene glycol esters of fatty acids, wherein the fatty acids for example comprise a fatty acid selected from the group consisting of lauric, palmitic, oleic, and stearic acids.

In other detailed aspects of the invention, topical delivery of an anti-aging effective compound (e.g., Coenzyme Q10) is enhanced by combining or coordinately administering the anti-aging compound (e.g., Coenzyme Q10) with a polypropylene-based or other membrane penetration-enhancing polymer or copolymer (e.g., a polypropylene glycol- (PPG)-PEG copolymer). A variety of such polymers (e.g., polypropylene oxides, polypropylene glycols) are known in the art and can provide for enhanced membrane permeation of anti-aging effective compounds (see e.g., Vandorpe et al., Biomaterials 18: 1147-1152, 1997; Kajihara et al., Biosci. Biotechnol. Biochem. 61: 197-199, 1997; Yeh et al., Pharm. Res. 13: 1693-1698, 1996; Rogers et al., J. Chromatogr. B. Biomed. Appl. 680: 231-236, 1996; Kronick, Pharmacol. Res. Commun. 10: 257-259, 1978, each incorporated herein by reference.)

BIOADHESIVE DELIVERY VEHICLES AND METHODS

In additional aspects of the invention, the anti-aging effective compound to be delivered by a facial skin patch 10 or mask 12 of the invention are formulated or coordinately administered with a nontoxic bioadhesive to enhance topical delivery of the anti-aging effective compound. In certain embodiments, safe and effective bioadhesive are formulated directly with the anti-aging effective compound(s) and applied to the patch or mask undersurface 18, or invested in the patch or mask body 14, to enhance topical delivery of the anti-aging effective compound(s). The bioadhesive delivery vehicle may serve a dual purpose as a delivery vehicle and as an attachment means to mediate removable attachment of the patch or mask to the facial or neck skin area to be treated, to allow the patch or mask body to securely, removably to conform to the subject skin area. Alternatively, the bioadhesive may be applied to or invested in the patch or mask body separate from the anti-aging effective compound(s), to the same or different surface(s) or portions of the patch or mask body to which the anti-aging effective compound(s) is/are applied or invested.

Thus, in certain embodiments, the bioadhesive agent is admixed with the anti-aging effective compound and layered onto the undersurface 18 of the patch or mask body as an external formulation coating 160 (see, e.g., Fig. 7). Alternatively, the anti-aging effective compound can be initially applied (alone or admixed with a different carrier or delivery vehicle) to the undersurface separate from the bioadhesive agent as a first coating layer 162, and then the bioadhesive agent is applied over this coating as a second, adhesive coating layer 164. In other alternative embodiments, the anti-aging effective compound can be initially invested (alone or admixed with a different carrier or delivery vehicle) into all or part of the patch or mask body 14 in chemical communication with the undersurface thereof (e.g., by absorbing, adsorbing, infusing, injecting, integrally molding, encapsulating, etc., to invest the anti-aging compound in all or part of the patch body) to separate from the bioadhesive agent as an invested layer 170 or infiltrate, and then the bioadhesive agent is applied or otherwise contacted with the undersurface to provide a separate adhesive coating layer 172 (see, e.g., Fig. 8). When the anti-aging effective compound(s) are invested in the patch or mask body in this manner, they may be loaded as described above to penetrate to a desired depth or width of the patch or mask body (as depicted in Fig. 8). The depth of penetration 174 in this regard allows for selective loading of the patch or mask body with a predetermined amount of the anti-aging effective compound, and further provides for additional control over the rate and duration of delivery of the anti-aging effective compound. Often, the anti-aging effective compound is loaded to penetrate one-fourth to one-half or more of the total depth or thickness of the patch or mask body 14, which may be directed across the entire body or at one or more selected loading point(s) (typically where the patch or mask contacts the facial or neck skin to be treated, for example at one or more drug delivery section(s) such as a supraorbital 62, infraorbital 64, lateral orbital 66 or medial orbital drug delivery section, or at any other surface-contacting feature). In this manner, the reservoir function of the patch or mask body can be controlled and calibrated for controlled release and delivery of the anti-aging compound, as well as to direct delivery to selected target sites of the facial or neck skin, such as the orbital marginal area 30 or portions thereof.

As also depicted in figure 8, the facial skin patch 10 or mask12 of the invention may be packaged in any suitable enclosure, preferably a sealed enclosure, and will often be provided with a protective cover 175, such as a plastic sheet, tab, or tape applied to the undersurface 18 of the patch or mask body, or covering the external

formulation coating 160, and/or the adhesive coating layer 164. The protective cover may be provided with an adhesive to adhere in place or will alternatively adhere by removable bonding to the adhesive coating layer, and protects the undersurface and other portions of the patch or mask and the medicament from contamination and/or leakage or transfer of the medicament and other materials from the patch or mask. The protective cover may completely envelop the patch or mask body, or may be applied at the undersurface only, and is readily removed by tearing and/or peeling of the cover away from the opposing patch or mask surface(s).

In further embodiments of the invention, the rate, duration and/or location of delivery of the anti-aging effective compound is/are additionally controlled by varying the construction of the patch 10 or mask 12 body 14. For example, the fibrous or porous composition or makeup of the patch or mask body can provide a gradient of pore or channel size, density or orientation, hydrophobicity, hydrophilicity, or other physicochemical parameters, normal (i.e., generally perpendicular to) the patch or mask undersurface 18 that selectively wicks, channels, expels, or otherwise directs, delivery of the anti-aging compound toward the undersurface 18 of the patch or mask body to come in contact with the skin to be treated. For example, the patch or mask body may feature a pore (e.g., open celled polymer cell) size gradient between an outer patch or mask body surface 176 and the undersurface, that serves to drive or transfer an anti-aging compound deeply imbued within the patch or mask body in the direction of the undersurface to facilitate controlled, prolonged delivery of the anti-aging compound to the target skin surface.

The bioadhesive, whether admixed with the anti-aging effective compound or applied as a separate layer, is permeable to diffusion and other chemical transport of the anti-aging effective compound to allow passage of the active compound through or from the bioadhesive to the target skin surface to permit effective, controlled delivery of the active compound as described above. In yet additional embodiments, the bioadhesive agent may be applied to selected portions of the patch or mask, for example to the undersurfaces 18' of individual patch or mask sections (see, e.g., Fig.s 5 and 6), to a circumferential ridge 180 extending from a peripheral undersurface 18'' of an orbital patch 24 or orbital mask 26 body to conform (in a circular or oval shape) to an entire orbital margin 30 of a subject (see, e.g., Fig. 7), or to any other anatomically conforming surface

feature (e.g., edge, margin, ridge, protrusion, etc.) to direct adhesion of the patch to specific facial or neck skin surface features for attachment.

Bioadhesive materials for use within the invention are optionally effective as attachment means to removably affix the patch 10 or mask 12 to a facial or neck skin area, with sufficient integrity of adhesion to secure the patch for prolonged periods as indicated above and in certain embodiments to resist dislodgement of the patch when subjected to facial skin movements in the subject skin area(s) to be treated. At the same time, the bioadhesive provides a suitable level of adhesion to allow removal of the patch or mask, typically without the aid of solvents, without unacceptable discomfort to the subject. Various polymers, both natural and synthetic ones, show acceptable binding to skin surfaces under physiological conditions. The strength of this interaction can readily be measured by mechanical peel or shear tests. A variety of suitable test methods and instruments to serve such purposes are known in the art (see, e.g., Gu et al., Crit. Rev. Ther. Drug Carrier Syst. 5:21-67, 1988; Duchene et al., Drug Dev. Ind. Pharm. 14:283-318, 1988, incorporated herein by reference). When applied to a humid skin surface, many dry materials will spontaneously adhere, at least slightly. After such an initial contact, some hydrophilic materials start to attract water by adsorption, swelling or capillary forces, and if this water is absorbed from the underlying substrate or from the polymer-tissue interface, the adhesion may be appropriate to achieve the functions of the invention (see, e.g., Al-Dujaili et al., Int. J. Pharm. 34:75-79, 1986; Marvola et al., J. Pharm. Sci. 72:1034-1036, 1983; Marvola et al., J. Pharm. Sci. 71:975-977, 1982; and Swisher et al., Int. J. Pharm. 22:219, 1984; Chen, et al., Adhesion in Biological Systems, p. 172, Manly, Ed., Academic Press, London, 1970, each incorporated herein by reference). Such 'adhesion by hydration' can be quite strong, but formulations adapted to employ this mechanism must account for swelling which continues as the dosage transforms into a hydrated skin. This is projected for many hydrocolloids useful within the invention, especially some cellulose-derivatives, which are generally non-adhesive when applied in pre-hydrated state. Nevertheless, bioadhesive drug delivery systems for topical administration are effective within the invention when such materials are applied in the form of a dry polymeric powder, microsphere, or film-type delivery form.

Other polymers useful within the invention adhere to skin surfaces not only when applied in dry, but also in fully hydrated state, and in the presence of excess amounts

of water. The selection of a bioadhesive thus requires due consideration of the conditions, physiological as well as physico-chemical, under which the contact to the skin will be formed and maintained. In particular, the amount of water or humidity usually present at the intended site of adhesion, and the prevailing pH, are known to largely affect the mucoadhesive binding strength of different polymers.

Several polymeric bioadhesive drug delivery systems are known in the art and useful within the methods and devices of the invention (see, e.g., U.S. Pat. No.s 3,972,995; 4,259,314; 4,680,323; 4,740,365; 4,573,996; 4,292,299; 4,715,369; 4,876,092; 4,855,142; 4,250,163; 4,226,848; 4,948,580; U.S. Pat. Reissue 33,093; and Robinson, 18 Proc. Intern. Symp. Control. Rel. Bioact. Mater. 75 (1991), each incorporated herein by reference). The potential of various bioadhesive polymers as a topical delivery platform within the methods and devices of the invention can be readily assessed by determining their ability to retain and release a specific anti-aging effective compound, e.g., a therapeutic anti-oxidant compound, as well as by their capacity to interact with skin surfaces following incorporation of the active agent therein. In addition, well known methods will be applied to determine the biocompatibility of selected polymers with the tissue at the site of topical administration. One aspect of polymer biocompatibility is the potential effect for the polymer to induce a cytokine response. In certain circumstances, implanted polymers have been shown to induce the release of inflammatory cytokines from adhering cells, such as monocytes and macrophages. Similar potential adverse reactions of epidermal and associated cells in contact with candidate bioadhesive polymers will be determined using routine *in vitro* and *in vivo* assays to measure biocompatibility of a selected polymer delivery platform.

Bioadhesion involves the attachment of a natural or synthetic polymer to a biological substrate. It serves within the methods and compositions of the invention as a practical method for drug immobilization or localization at the skin surface, thereby providing for enhanced absorption and better controlled drug delivery, and optionally as attachment means to affix a patch 10 or mask 12 of the invention to a target facial or neck skin area. The use of bioadhesive polymers within the invention provides for maintenance of a relatively constant effective drug concentration at the target site for action for an extended time period. For optimal performance, drug concentrations at the target site (e.g., a selected facial or neck skin surface or basal layer or associated tissue or extracellular

compartment)) should be maintained above the effective concentration level for the drug and below a toxic or otherwise excessive dosage level. Bioadhesive and other delivery components within the methods and devices of the invention can improve the effectiveness of a treatment by helping maintain the drug concentration between effective and toxic levels, by inhibiting dilution of the drug away from the delivery point, and improving targeting and localization of the drug. In this context, bioadhesion increases the intimacy and duration of contact between a drug-containing polymer and the skin surface. The combined effects of this enhanced, direct drug absorption, and the decrease in excretion rate that results from reduced diffusion and improved localization, significantly enhances bioavailability of the drug and allows for a smaller dosage and less frequent administration.

Exemplary bioadhesives for use within certain embodiments of the invention include acrylic-based hydrogels, which are well-suited for bioadhesion due to their flexibility and nonabrasive characteristics in the partially swollen state to reduce damage-causing attrition to the tissues in contact (Park et al., J. Control. Release 2:47-57, 1985, incorporated herein by reference). Furthermore, their high permeability in the swollen state allows unreacted monomer, un-crosslinked polymer chains, and the initiator to be washed out of the matrix after polymerization, which is a desirable feature for bioadhesive materials for use within the invention. Acrylic-based polymer devices exhibit very high adhesive bond strength, as determined by various known methods (Park et al., J. Control. Release 2:47-57, 1985; Park et al., Pharm. Res. 4:457-464, 1987; and Ch'ng et al., J. Pharm. Sci. 74:399-405, 1985, each incorporated herein by reference).

For controlled topical delivery of anti-aging effective compounds, bioadhesive polymeric delivery vehicles may also function in part to shield the anti-aging effective compound from degradation or enzymatic breakdown, while at the same time providing for enhanced penetration of the anti-oxidant compound into or through the skin. In this context, bioadhesive polymers have demonstrated considerable potential for enhancing topical drug delivery. As an example, the bioavailability of 9-desglycinamide, 8-arginine vasopressin (DGAVP) intraduodenally administered to rats together with a 1% (w/v) saline dispersion of the mucoadhesive poly(acrylic acid) derivative polycarbophil, was 3-5-fold increased compared to an aqueous solution of the peptide drug without this polymer (Lehr et al., J. Pharm. Pharmacol.44:402-407, 1992, incorporated herein by

reference). In this study, the drug was not bound to or otherwise integrally associated with the mucoadhesive polymer in the formulation, which would therefore not be expected to yield enhanced peptide absorption via prolonged residence time or intensified contact to the mucosal surface. Thus, certain bioadhesive polymers for use within the invention will directly enhance the permeability of the skin absorption barrier in part by protecting the active agent, e.g., peptide or protein, from enzymatic degradation.

Another useful bioadhesive agent within the methods and devices of the invention is chitosan, as well as its analogs and derivatives. Chitosan is a non-toxic, biocompatible and biodegradable polymer that is widely used for pharmaceutical and medical applications because of its favorable properties of low toxicity and good biocompatibility (Yomota, Pharm. Tech. Japan 10:557-564, 1994, incorporated herein by reference). It is a natural polyaminosaccharide prepared from chitin by N-deacetylation with alkali. A wide variety of biomedical uses for chitosan have been reported over the last two decades, based for example on its reported wound healing, antimicrobial and hemostatic properties (Kas, J. Microencapsulation 14:689-711, 1997, incorporated herein by reference). Chitosan has also been used as a pharmaceutical excipient in conventional dosage forms as well as in novel applications involving bioadhesion and transmucosal drug transport (Illum, Pharm. Res. 15:1326-1331, 1998; and Olsen et al., Chitin and Chitosan-sources, Chemistry, Biochemistry, Physical Properties and Applications, pp. 813-828, Skjak-Braek et al., Eds., Elsevier, London, 1989, each incorporated herein by reference). Furthermore, chitosan has been reported to promote absorption of small polar molecules and peptide and protein drugs through nasal mucosa in animal models and human volunteers (Illum et al., Pharm. Res.11:1186-1189, 1994, incorporated herein by reference). Other studies have shown an enhancing effect on penetration of compounds across the intestinal mucosa and cultured Caco-2 cells (Schipper et al., Pharm. res. 14:23-29, 1997; and Kotze et al., Int. J. Pharm. 159:243-253, 1997, each incorporated herein by reference). Chitosan has also been proposed as a bioadhesive polymer for use in topical drug delivery (Miyazaki et al., Biol. Pharm. Bull. 17:745-747, 1994; Ikinci et al., Advances in Chitin Science, Vol. 4, Peter et al., Eds., University of Potsdam, in press; Senel, et al., Int. J. Pharm. 193:197-203, 2000; Needleman, et al., J. Clin. Periodontol.24:394-400, 1997, each incorporated herein by reference). Initial studies showed that chitosan has an extended retention time on the oral mucosa (Needleman et al., J. Clin. Periodontol. 25:74-82, 1998) and with its antimicrobial properties and

biocompatibility is an excellent candidate for the treatment of oral mucositis. More recently, Senel et al., Biomaterials 21:2067-2071, 2000 (incorporated herein by reference) reported that chitosan provides an effective gel carrier for delivery of the bioactive peptide, transforming growth factor-β (TGF-β).

As used within the methods and compositions of the invention, chitosan increases the retention of anti-aging effective compounds at a topical site of application. This is thought to be mediated in part by a positive charge characteristic of chitosan, which may influence tissue permeability even after physical removal of chitosan from the surface (Schipper et al., Pharm. Res. 14:23-29, 1997, incorporated herein by reference). Chitosan may also increase the thermodynamic activity of other absorption-promoting agents used in certain formulations of the invention, resulting in enhanced penetration. Lastly, as chitosan has been reported to disrupt lipid micelles in the intestine (Muzzarelli et al., EUCHIS'99, Third International Conference of the European Chitin Society, Abstract Book , ORAD-PS-059, Potsdam, Germany, 1999), its absorption-promoting effects may be due in part to its interference with the lipid organization in tissues.

As with other bioadhesive gels provided herein, the use of chitosan can reduce the frequency of application and the amount of anti-aging effective compound administered while yielding an effective delivery amount or dose. This mode of administration can also improve patient compliance and acceptance. The occlusion and lubrication of chitosan and other bioadhesive gels is expected to reduce any discomfort that may arise from inflammatory, allergic and ulcerative conditions of the skin. In addition, chitosan acts non-specifically on certain deleterious microorganisms, including fungi (Knapczyk, Chitin World, pp. 504-511, Karnicki et al., Eds., Wirtschaftverlag NW, Germany, 1994, incorporated herein by reference), and may also beneficially stimulate cell proliferation and tissue organization by acting as an inductive primer to repair and physiologically rebuild damaged tissue (Muzzarelli et al. (Biomaterials 10:598-603, 1989, incorporated herein by reference).

The foregoing bioadhesive agents are useful within the methods and devices of the instant invention, which optionally incorporate an effective amount and form of a bioadhesive agent to prolong persistence or otherwise increase topical absorption of anti-aging effective compounds. The bioadhesive agents may be coordinately administered as adjunct compounds (i.e., separately applied before or after application of

the facial patch 10 or mask 12) or as additives to or carriers for the anti-aging effective compound(s). In certain embodiments, the bioadhesive agent acts as a 'pharmaceutical glue' to provide attachment means for the patch or mask, whereas in other embodiments adjunct delivery or combinatorial formulation of the bioadhesive agent serves to intensify contact of the anti-aging effective compound with the skin, in some cases by increasing skin permeability to significantly increase the drug concentration gradient measured at a target site of delivery (e.g., the basal layer of the treated skin). Yet additional bioadhesive agents for use within the invention act as enzyme inhibitors to enhance the stability of topically administered anti-aging effective compounds coordinately or combinatorially applied with the bioadhesive agent.

Bioadhesive agents and other "delivery vehicles" and carriers for use within the invention maintain a desired concentration gradient of the anti-aging effective compound across the skin to ensure penetration of even large molecules into or through the skin. Typically, employment of bioadhesives and other delivery or penetration-enhancing agents within the methods and devices of the invention yields a two- to five-fold, often a five- to ten-fold increase in permeability for anti-aging effective compounds (e.g., anti-oxidant compounds), into or through the skin. This enhancement of permeation often permits effective topical delivery of anti-aging compounds to the basal portion of the epidermis or even into the extracellular compartments or systemic circulation underlying the skin.

This enhanced delivery provides for greatly improved effectiveness of delivery of anti-aging effective compounds (e.g., anti-oxidant compounds). These results will depend in part on the hydrophilicity of the compound, whereby greater penetration will be achieved with hydrophilic species compared to water insoluble compounds. In addition to these effects, employment of bioadhesives and other delivery-enhancing agents to increase drug persistence at the skin surface can provide a reservoir function for prolonged drug delivery, whereby compounds not only penetrate across the skin but also back-diffuse toward the skin surface once the material at the surface is depleted.

In various embodiments, the methods and devices of the instant invention optionally incorporate bioadhesive materials that yield prolonged residence time at the skin surface or target site of action of the anti-aging effective compound. Alternatively, the bioadhesive material may otherwise facilitate topical absorption by the skin of the anti-

aging effective compound, e.g., by facilitating localization of the active agent to a selected target site of activity. In additional aspects, adjunct delivery or combinatorial formulation of a bioadhesive agent within the methods and devices of the invention intensify contact of the anti-aging effective compound with the skin, in some instances including by increasing skin permeability, (e.g., to effectively increase the drug concentration gradient). In further alternate embodiments, bioadhesives and other polymers disclosed herein serve to inhibit proteolytic or other enzymes that might degrade the anti-aging effective compound. For a review of different approaches to bioadhesion that are useful within the methods and devices of the invention, see, e.g., Lehr C. M., Eur J. Drug Metab. Pharmacokinetics 21(2):139-148, 1996 (incorporated herein by reference).

LIPOSOMES AND MICELLAR DELIVERY VEHICLES

The methods and devices of the instant invention optionally incorporate effective lipid or fatty acid based carriers, processing agents, or delivery vehicles, to provide improved formulations for topical delivery of anti-aging effective compounds. For example, a variety of formulations and methods are provided for topical delivery which comprise an anti-aging effective compound, such as a anti-oxidant compound, admixed with or encapsulated by, or coordinately administered with, a liposome, mixed micellar carrier, or emulsion, to enhance chemical and physical stability and increase the half life of the anti-aging effective compound (e.g., by reducing susceptibility to enzymatic degradation or chemical modification) upon topical delivery.

Within certain aspects of the invention, specialized delivery systems for anti-aging effective compounds comprise small lipid vesicles known as liposomes (see, e.g., Chonn et al., Curr. Opin. Biotechnol. 6:698-708, 1995; Lasic, Trends Biotechnol. 16:307-321, 1998; and Gregoriadis, Trends Biotechnol. 13:527-537, 1995, each incorporated herein by reference). These are typically made from natural, biodegradable, non-toxic, and non-immunogenic lipid molecules, and can efficiently entrap or bind drug molecules, including anti-aging effective compounds (e.g., anti-oxidant compounds), proteins, or peptides, into, or onto, their membranes. The attractiveness of liposomes as a delivery vehicle or carrier for anti-aging effective compounds within the invention is increased by the fact that the encapsulated anti-aging compounds can remain in their

preferred aqueous environment within the vesicles, while the liposomal membrane protects them against degradation and other destabilizing factors. Even though not all liposome preparation methods known are feasible in the encapsulation of anti-aging effective compounds (e.g., anti-oxidant compounds) due to their specific physical and chemical properties, several methods allow the encapsulation of these macromolecules without substantial deactivation (see, e.g., Weiner, Immunomethods 4:201-209, 1994, incorporated herein by reference).

A variety of additional methods are available for preparing liposomes for use within the invention (e.g., as described in Szoka et al., Ann. Rev. Biophys. Bioeng. 9:467, 1980; and U.S. Pat. Nos. 4,235,871, 4,501,728, and 4,837,028, each incorporated herein by reference). For use with liposome delivery, the anti-aging effective compound is typically entrapped within the liposome, or lipid vesicle, or is bound to the outside of the vesicle. Several strategies have been devised to increase the effectiveness of liposome-mediated delivery by targeting liposomes to specific tissues and specific cell types. Liposome formulations, including those containing a cationic lipid, have been shown to be safe and well tolerated in human patients (Treat et al., J. Natl. Cancer Instit 82:1706-1710, 1990, incorporated herein by reference).

Like liposomes, unsaturated long chain fatty acids, which also have enhancing activity for tissue absorption, can form closed vesicles with bilayer-like structures (so called "ufasomes") to provide a carrier or delivery vehicle for anti-aging effective compounds. These can be formed, for example, using oleic acid to entrap biologically active anti-oxidant compounds for topical delivery within the invention.

Other delivery systems for use within the invention combine the use of polymers and liposomes. Exemplifying this type of hybrid delivery system, liposomes containing the model protein horseradish peroxidase (HRP) have been effectively encapsulated inside the natural polymer fibrin (Henschen et al., Blood Coagulation, pp. 171-241, Zwaal, et al., Eds., Elsevier, Amsterdam, 1986, incorporated herein by reference). Because of its biocompatibility and biodegradability, fibrin is a useful polymer matrix for drug delivery systems in this context (see, e.g., Senderoff, et al., J. Parenter. Sci. Technol. 45:2-6, 1991; and Jackson, Nat. Med 2:637-638, 1996, incorporated herein by reference). In addition, release of anti-aging effective compounds from this delivery system is controllable through the extent of covalent crosslinking and the addition of

antifibrinolytic agents to the fibrin polymer (Uchino et al., Fibrinolysis 5:93-98, 1991, incorporated herein by reference).

Additional delivery vehicles or carriers for use within the invention include long and medium chain fatty acids, as well as surfactant mixed micelles with fatty acids (see, e.g., Muranishi, Crit. Rev. Ther. Drug Carrier Syst. 7:1-33, 1990, incorporated herein by reference). Free fatty acids and their monoglycerides which have polar groups attached have been demonstrated in the form of mixed micelles to act on tissue barrier as penetration enhancers. This discovery of barrier modifying function of free fatty acids (carboxylic acids with a chain length varying from 12 to 20 carbon atoms) and their polar derivatives has stimulated extensive research on the application of these agents as absorption enhancers.

For use within the methods of the invention, long chain fatty acids, especially fusogenic lipids (unsaturated fatty acids and monoglycerides such as oleic acid, linoleic acid, linoleic acid, monoolein, etc.) provide useful carriers to enhance topical delivery of anti-aging effective compounds. Medium chain fatty acids (C6 to C12) and monoglycerides have also been shown to have enhancing activity in intestinal drug absorption and can be adapted for use within the topical delivery methods and devices of the invention. In addition, sodium salts of medium and long chain fatty acids are effective delivery vehicles and absorption-enhancing agents for topical delivery of anti-aging effective compounds within the invention. Thus, fatty acids can be employed in soluble forms of sodium salts or by the addition of non-toxic surfactants, e.g., polyoxyethylated hydrogenated castor oil, sodium taurocholate, etc. Mixed micelles of naturally occurring unsaturated long chain fatty acids (oleic acid or linoleic acid) and their monoglycerides with bile salts have been shown to exhibit absorption-enhancing abilities in the intestinal mucosa (see, e.g., Muranishi, Pharm. Res. 2:108-118, 1985; and Crit. Rev. Ther. drug carrier Syst. 7:1-33, 1990, each incorporated herein by reference). Other fatty acid and mixed micellar preparations that are useful within the invention include, but are not limited to, Na caprylate (C8), Na caprate (C10), Na laurate (C12) or Na oleate (C18), optionally combined with bile salts, such as glycocholate and taurocholate.

SURFACE ACTIVE AGENTS AND METHODS

Within more detailed aspects of the invention, one or more membrane penetration-enhancing agents may be employed within the methods and devices of the invention to enhance topical delivery of an anti-aging effective compound (e.g., an anti-oxidant such as coenzyme Q10). Membrane penetration enhancing agents in this context can be selected from: a surfactant; a bile salt; a phospholipid additive; mixed micelle; liposome, or carrier; an alcohol; an enamine; a long-chain amphipathic molecule; a small hydrophobic penetration enhancer; sodium or a salicylic acid derivative; a glycerol ester of acetoacetic acid; a clyclodextrin or beta-cyclodextrin derivative; a medium-chain fatty acid; a chelating agent; an amino acid or salt thereof; or any combination of the foregoing membrane penetration enhancing agents.

Certain surface-active agents are readily incorporated within the topical delivery formulations and methods of the invention as topical absorption enhancing agents. These agents, which may be coordinately administered or combinatorially formulated with anti-aging effective compounds of the invention, may be selected from a broad assemblage of known surfactants. Surfactants, which generally fall into three classes: (1) nonionic polyoxyethylene ethers; (2) bile salts such as sodium glycocholate (SGC) and deoxycholate (DOC); and (3) derivatives of fusidic acid such as sodium taurodihydrofusidate (STDHF). The mechanisms of action of these various classes of surface active agents typically include solubilization of the anti-aging effective compound. Within exemplary embodiments of the invention, one or more surface active agents is coordinately administered or combinatorially formulated with an anti-aging compound, for example Coenzyme Q10, in an amount effective to enhance skin absorption of the anti-aging effective compound while not substantially adversely effecting the biological activity of this or other active agent(s) nor causing substantial adverse side effects (e.g., undesirable skin irritation). Exemplary surface active agents within specific aspects of the invention include, but are not limited to, non-ionic surfactants, such as polysorbates (e.g., polysorbate 80), polyoxyethylene lauryl ether, *n*-lauryl-β-D-maltopyranoside (LM), cetyl ether, stearyl ether, and nonylphenyl ether, and other surfactants, such as sodium lauryl sulfate, sodium taurochloate, sodium cholate, sodium glycocholate, L-carnitine, and saponin. Also included are different classes ofsurfactants disclosed elsewhere herein, for example detergents (e.g., Tween 80, Triton X-100) and fatty acid-surfactants (e.g., linoleic acid), which may be used alone or as mixed micellar components. In more detailed aspects of the invention, laureth-9 is employed as a surfactant within the methods and

formulations of the invention (see, e.g., Hirai et al., Intl. J. Pharmaceutics 1;173-184, 1981; G.B. Patent specification 1 527 605; and Salzman et al., New Eng. J. Med., April, 1985, 1078-1084, each incorporated herein by reference).

FORMULATIONS AND ADDITIVES

The anti-aging effective compounds for use within the methods and devices of the invention can be formulated in a variety of suitable carriers and forms, including but not limited to polymeric delivery vehicles, hydrogels, biodegradable polymers, matrices, sprays, pastes, gels, ointments, suspensions, emulsions, creams, lotions, unguents, solutions, suspensions, emulsions, powders, and the like. Exemplary formulations include aqueous or alcoholic solutions, aqueous suspensions, emulsions, ointments, creams, oils, or powders.

Depending on the desired formulation, the anti-aging compounds can be incorporated into pharmaceutical and/or cosmetic bases for topical applications, which formulations may optionally comprise as additional components, for example, oil components, fats and waxes, emulsifiers, anionic, cationic, ampholytic, zwitterionic and/or nonionic surfactants, lower mono- and polyhydric alcohols, water, preservatives, buffer substances, thickeners, fragrances, dyestuffs and opacifying agents. The active substances according to the invention can also advantageously be used in transdermal therapeutic systems, in particular cubic systems.

Alternative formulations of the anti-aging effective compound for application or incorporation to or within a facial patch 10 or mask 12 of the invention may provide additional desired effects in the skin, including such effects as smoothing, lubricating, glossing, coloring and masking of the skin. In certain embodiments, it may be further desired to add to the formulations one or more substance(s) that modify cellular energy metabolism, for example cellular energy transfer agents (such as creatine, guanine, guanosine, adenine, adenosine, nicotine, nicotinamide or riboflavin), coenzymes (for example pantothenic acid, panthenol, lipoic acid or niacin), auxiliary factors (for example L-carnitine, dolichol or uridine), substrates (for example hexoses, pentoses or fatty acids) and intermediate metabolism products (for example citric acid or pyruvate) and/or glutathione.

Yet additional methods and devices of the invention advantageously incorporate substances that absorb UV radiation in the UVA and/or in the UVB region and provide a sunscreen and/or additional anti-oxidant effect. Examples of oil-soluble UVB filtering agents that are useful within the invention include 3-benylidenecamphor derivatives, for example 3-(4-methylbenzylidene)camphor and 3-benzylidenecamphor. Examples of useful water-soluble UVB filters include salts of 2-phenylbenzimidazole-5-sulphonic acid, such as its sodium, potassium or its triethanolammonium salt, and the sulphonic acid itself. Useful UVA filters include derivatives of dibenzoylmethane, for example 1-(4'-tert-butylphenyl)-3-(4'-methoxyphenyl)propane-1,3-dione and 1-phenyl-3-(4'-isopropylphenyl)propane-1,3-dione.

In other embodiment, an abrasive substance may be included within the methods and devices of the invention. The inclusion of an abrasive substance promotes removal of dead or damaged intervening tissue and makes the underlying tissue more accessible to the therapeutic action of anti-aging compounds. Those of skill in the art will recognize that many appropriate abrasive substances are known and may be used in the practice of the instant invention. Useful examples include, but are not limited to, ground fruit pits, ground nut kernels, ground nut shells, grain hulls (from for example wheat, bran, oats, rice, etc.), saw dust, aluminum oxide, silica sand, pumice, plastic and acrylic grit, plastic flour, and ground corn cobs.

THERMAL PATCHES AND MASKS

In yet additional embodiments of the invention, the facial patch 10 or mask 12 comprises a separate or integral, self-contained or externally charged thermal element 190. The thermal element can function as a heating element to facilitate delivery and activity of the anti-aging effective compound by increasing the temperature at a target skin area, thereby increasing chemical kinetic factors as well as circulation in and around the subject skin areas to be treated. This increases or accelerates the extent or rate of therapeutic efficacy of the facial patch or mask as described above, while increasing comfort for the subject.

The thermal element 190 may be externally connected to the patch or mask simply by placing the heating element in contact with an outer surface 176 of the patch,

but more typically by a thermal element attachment means 200 that attaches the thermal element to the patch or mask outer surface (see, e.g., Fig. 9). For example, the thermal element can be permanently bonded to the patch or mask outer surface by gluing, welding, stitching, or the like. Alternatively, the thermal element can be removably attached by any suitable closure/release device such as opposing hook and loop (e.g., VELCRO®) material, snaps, ties, and the like. In certain embodiments, the thermal element is removably attached to the patch or mask to allow replacement or repeated charging of the thermal element and subsequent reattachment of the thermal element to the patch or mask.

In alternative embodiments, the thermal element 190 may be integrally connected to the patch or mask body, for example by enclosure of the thermal element within a pocket 202 defined within the patch or mask body or other layer of the patch or mask (see, e.g., Fig.s 10 and 11). The thermal element may thus be enclosed within the patch or mask, permanently or removably. In the embodiment shown in Fig. 10, the thermal element is removably enclosed within a pocket enclosed within the patch body, which pocket is accessible for removal of the thermal element for replacement or recharging by way of a releasable closure 202 (e.g., a zippered or velcroed seam) of the pocket.

The shape of the thermal element 190 and the shape of the pocket 202 when the thermal element is an integral element can vary, e.g., from a square, rectangular, band, or circular shape. Preferably, the thermal element and optional pocket is/are anatomically shaped and dimensioned in approximately parallel shape and dimension with anatomical features of the patch 10 or mask 12, so that the thermal element substantially extends across all or most of the skin area to be treated. This relationship is well depicted in Fig. 11, wherein the heating element is contained in a pocket 202 of an orbital patch 24 that is defined by a circumferential ridge 180 extending from a peripheral undersurface 18'' of the orbital patch body 14 to conform (in a circular or oval shape) to an entire orbital margin 30 of a subject. Other thermal elements will thus typically parallel the outline of an entire patch or mask upper surface, or of one or more anatomically configured patch or mask sections or surface ridges or protrusions as described above.

With regard to selection of thermal elements 190, a variety of useful self-contained or externally powered heating and/or cooling elements are known in the art for use within the methods and devices of the invention. For example, electrical heating and

cooling elements may be employed that use internal or external, battery or central power sources. More preferable are less bulky, self-contained heating or cooling elements, such as chemical and thermal gel heating and/or cooling elements. Chemical heating elements are available in a variety of compositions and forms, and are typically activated for a single use. These chemical heating elements are easily incorporated within the facial patches 10 and masks 12 of the invention, and may be activated, for example by exposing an exothermic chemical in a chemical heat pack to air.

In certain embodiments of the invention, a rechargeable thermal gel is employed as the thermal element 190. Thermal gels are well known in the art for their use in rechargeable heating and/or cooling packs for prosthetic and therapeutic use. A thermal gel efficiently stores and transmits heat in one mode of use, and can be effectively cooled to absorb heat in an alternate mode of use. Attachment or integration of a thermal gel thermal element with the facial patches 10 and masks 12 of the invention is therefore contemplated to serve dual or alternate purposes of providing a rechargeable heat source for enhancing function of the patch or mask as described above, and optionally a rechargeable cooling source to alleviate facial swelling and/or pain in other applications.

A thermal gel can be employed as a thermal element 190 for use within the invention in a variety of ways. The gel can be injected or otherwise incorporated in an integral pocket within the patch 10 or mask 12 (e.g., orbital mask 26) body 14, as shown in Fig. 11, provided the pocket is impervious to leakage of the gel. Alternatively, a separate gel pack comprising a flexible bladder 220 enclosing a volume of thermal gel 222 (see, Fig. 10) may be removably or permanently attached to the patch or mask or incorporated in the patch or mask body as described above. A useful construction in this regard employs a single layer bladder constructed of flexible, durable material that is resistant to heat, cold, and rupture. A lumen of the bladder is filled with and sealably encloses a thermal gel adapted for repeated heating and cooling. The bladder may be fabricated from a variety of materials having suitable flexibility, strength and durability to provide a supple, flexible feel when the gel pack is attached to or incorporated within the patch or mask and the patch or mask is applied to the facial skin area to be treated. Suitable materials in this context include, for example, vinyl plastics, silicon plastics (e.g, silastic materials used for breast implants), latex or other like materials, provided the materials are heat stable (e.g., upon heating in warm water or microwaving). It is particularly preferred

that the material used to construct the gel pack bladder be expandable in order to allow for the escape of steam from the lumen of the bladder to the outside (i.e., through microscopic interstices in the bladder material) to prevent explosion of the bladder in the event of overheating.

In one exemplary embodiment of the invention, the gel pack bladder 220 is constructed of a vinyl or silicon plastic material cut into upper and lower sheets each having a marginal outline corresponding generally to, but slightly smaller than, a circumferential margin of the pocket 202. The two bladder sheets are annealed together, e.g., by gluing or heat sealing, along most of the marginal outline of the gel pack, leaving a small filling aperture between the two sheets for filling the bladder with gel. Gel is then protruded through the filling opening into the lumen of the bladder formed between the two sheets, and the bladder is closed by heat sealing or otherwise annealing the two sheets together at the site of the filling aperture.

The gel pack functions as a non-chemical, non-electrical and non-fuel burning heating element which retains and transmits heat energy or cold to the face of the wearer. Notably, the gel pack has an adjustable heating capacity adapted to therapeutic and related uses associated with a range of activities (including activities undertaken in a warm or cold environment). Briefly, the temperature and time period of heating or cooling of the gel pack dictates the level and duration at which the gel pack transmits heat or cold to the face of the wearer, whereby a broad spectrum of heating or cooling levels and times can be selected by the user. The gel pack is further adapted for fast, safe, and repeatable heating or cooling, whereby the pack may be recharged repeatedly during long-term use, for example to provide continued therapeutic benefit during extended activities.

A variety of gels are known in the art which are specifically adapted for their ability to be cooled and heated over a wide range of temperatures and to maintain their physical characteristics, e.g., chemical integrity and pliability, during repeated heating and cooling. Many such gels are suitable for use within the invention, while specific gel characteristics may be selected for use within different embodiments of the invention. Thus, gels having a higher maximum heating tolerance may be selected for use with a monopiece face mask to alleviate symptoms of facial skin aging by application of an anti-aging effect compound. Alternatively, gels that maintain their physicochemical properties at very low temperatures may be selected for specific therapeutic uses, e.g., to

reduce inflammation in a subject's facial skin following surgery. In most cases, however, it is generally desirable for safety purposes to select a gel having a wide range of temperature tolerance, e.g., from about –20°C to about 160°C, to prevent decomposition of the gel or rupture of the gel pack bladder from exposure to low or high temperature extremes.

Preferred gels for use within the invention include gels containing a water soluble humectant invested within a polymeric matrix (e.g., polymers, copolymers, or terpolymers containing monomer moieties, such as acrylic acid or acrylamide monomers). Suitable humectants include glycerin, dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), among others. A preferred agent for the polymeric matrix is a commercially available acrylic acid polymer powder, e.g. Carbopol 940® (B.F. Goodrich Co.) Also included within the gel is a suitable cross-linking agent, for example, N,N methylene-bisacrylamide (MBA), N-methylolacrylamide, allyl methacrylate, or ethylene glycol dimethacryllate). Other agents are optionally included as well, such as, anti-freeze/boiling point elevators (e.g., propylene glycol), absorbants (e.g., starch-acrylonitrile graft copolymers), agents to suppress bacterial growth, and/or agents to enhance processibility or shelf life. It will be appreciated by persons skilled in the art that the consistency of the gel can be varied by selecting different polymeric materials and by varying the ratio of the polymer agent relative to the amount of humectant and/or cross-linking agent. To produce a soft gel the ratio of humectant to polymer should be high and/or a relatively low percentage of cross linking agent should be used. A firmer gel is produced by decreasing the humectant relative to polymer content and/or increasing the amount of cross-linking agent.

EXAMPLE I

Transdermal Delivery of CoQ_{10} to a Facial Skin Area

An exemplary orbital patch 24 for treatment of periorbital skin aging is covered on an undersurface 18 of the patch or invested within all or part of a porous body 14 of the patch with an anti-aging effective compound, CoQ_{10}, and the patch is attached to an orbital marginal 30 skin surface area of a suitable mammalian test subject. Within the present example, a porcine test subject is selected to demonstrate effective delivery of the

CoQ_{10} compound into and/or across the test subject skin (e.g., past the stratum corneum which acts as an effective barrier to many compounds when topically applied in the absence of the effective patch delivery methods and formulations of the invention). Porcine skin represents an accepted, reasonably correlative model to evaluate skin penetration properties of the patches and anti-aging compound formulations of the invention in other mammalian subjects, including humans. Levels of CoQ_{10} in the skin following application of the orbital patch are quantified by any of a variety of methods, for example high performance liquid chromatography (HPLC) of excised skin samples. (Lang et al., Anal. Biochem, 157: 106-116, 1986; Giovannini, et al., Int. J. Tiss. Reac., X(2) 103-105, 1988); Scalori, et al., Int. J. Tiss. Reac., XII(3) 149-154, 1990, each incorporated herein by reference). Within these and related protocols, an orbital or other facial or neck skin patch or mask of the invention applied for an extended period (e.g., 2-4 hours, 4-8 hours, or approximately 7- 8 hours) delivers CoQ_{10} (optionally formulated within a polymeric, ethanol, or other delivery vehicle or carrier) in a manner that achieves penetration of the CoQ_{10} into the stratum corneum, with at least 20%, often 30%-50% or more of the CoQ_{10} initially loaded onto or within the patch or mask body penetrating into viable (actively metabolic) layers of the epidermis, and in many embodiments, into the basal skin layer and/or dermis.

EXAMPLE II

Maximal Skin Concentration and Residence Time of CoQ_{10} Applied by Orbital Patch for Treatment of Periorbital Skin Aging in a Mammalian Subject

An ocular patch containing CoQ_{10} at a concentration of 1% or 10% in a polymeric delivery vehicle is applied in accordance with the above teachings for treatment of periorbital skin aging in a mammalian subject. Maximum concentrations of CoQ_{10} in the skin are measured in skin samples by means of high performance liquid chromatography (HPLC) (see, e.g., Lang et al., 1986; Giovannini, et al., 1988); Scalori, et al., 1990, each incorporated herein by reference). An ocular patch partially or completely imbued in the patch body with a formulation containing 1% or 10% CoQ_{10} is applied to the periorbital margin of a mammalian (e.g., porcine) subject to yield a maximum concentration of CoQ_{10} after application of the patch (e.g., as measured 1-2 hour after application) in the underlying skin of the subject of at least 1-5μg, and up to 5-15μg or

greater of CoQ_{10} per gram of skin as measured in a surface or basal layer of the skin. Residence time of detectable concentrations of CoQ_{10} following sustained application of the patch is at least 2-4, often 8 hours or more hours. Time release formulations as disclosed above extend residence time to at least 8 hours, up to 12 hours, 16 hours, 24 hours or longer.

EXAMPLE III

Facial Patch Delivery of CoQ_{10} Yields Antioxidant Effects in Human Skin

Oxidative events in human skin *in vivo* following delivery of CoQ_{10} via a facial patch or mask of the invention are detected, for example, by means of ultra weak photon emission assay [Sauermann et al.,. Oxidants & Antioxidants, Methods in Enzymology, L. Packer, ed., Academic Press, 300: 419-428 (1999), incorporated herein by reference]. In the basal state, cells emit low levels of photons. When UVA irradiation is applied there is an excited state with a large increase in the level of photons that decay with time. The level of photons emitted is an indication of the antioxidant status of the skin. If there is an increase in antioxidants, the excitation is less and the level of photons emitted will be reduced. The ultra weak photon emission (UPE) is measured after UVA irradiation in two age groups: (1) aged 18-25 years, (2) aged 60-72 years. The level of UPE in the skin is increased in the elderly group by approximately 33% indicating a reduction in the level of antioxidants, thus demonstrating that the level of antioxidants in the skin decreases with age.

To demonstrate that application of a facial patch or mask for delivery of CoQ_{10} (e.g., in a polymeric delivery vehicle) yields antioxidant effects *in vivo*, measurements are taken of the UPE of 13 volunteers (mean age 49 ± 6 years) treated with a facial patch or mask of the invention once or twice daily (for 2, 4, and 8 hours) for 7 days, for example using an orbital patch coated or imbued with 0.3% CoQ_{10}, or with a selected delivery vehicle alone as a control. Following exposure to 50 mJ/cm^2 UVA, the peri-orbital skin sites treated with the orbital patch will exhibit significantly lower levels (e.g., 20%, 30%, 40% reduced, and up to 50% reduced or lower levels) of UPE compared to a corresponding control level, indicating that the orbital patch containing CoQ_{10}

provides effective antioxidant activity *in vivo* to protect the peri-orbital skin against oxidative effects of UVA.

EXAMPLE IV

Facial Patch Delivery of CoQ_{10} Reduces Symptoms of Photoaging, Including Deep Wrinkles

A significant adverse symptom of photoaging is the presence of deep wrinkles. To demonstrate the efficacy of a facial skin patch of the invention delivering an anti-aging effective compound (e.g., CoQ_{10} in a polymeric delivery vehicle) against photoaging *in vivo,* an orbital or other facial skin area patch or mask containing 0.3% CoQ_{10} or vehicle control is applied to 20 elderly volunteers, once daily (e.g., around the peri-orbital skin of the eyes) for at least 2 hours each day and for test periods ranging from one week to one, two, three, and up to six months. In one exemplary protocol, an orbital patch containing CoQ_{10} in a delivery vehicle or carrier as described above is applied to one eye of a subject, and a control orbital patch containing a delivery vehicle alone is applied around the other eye. Casts are then prepared for quantitative microtopography [see, e.g., Hoppe, et al., J. Soc. Cosmetic Chemists 36: 105-123 (1985), incorporated herein by reference]. Photographs of the skin before treatment show deep wrinkles, which are characteristic of photoaging, whereas fine wrinkles are associated with chronological aging. Using microtopography to measure a reduction in the depth of wrinkles in aged skin, two important parameters can be calculated from the microtopography. They are: R_t which is the mean peak to valley measurement of a defined unit distance, andR_q which is the integrated area of the peaks and troughs. These measurements indicate the variation of the microtopography from a flat surface. Following treatment with an ocular patch of the invention delivering CoQ_{10}, the depth of these deep wrinkles will be significantly reduced (e.g., 20%, 30%, 40% reduced, and up to 50% reduced or better). In certain examples, treatment with an orbital patch containing 0.3% CoQ10 will results in at least a 25% reduction in the mean peak to valley depth of the skin and at least a 25% reduction in the R_q value, compared to controls.

EXAMPLE V

Facial Patch Delivery of CoQ_{10} Reduces Senile Xerosis

Although the stratum corneum, the outermost layer of the epidermis, is continuously sloughed off and replaced in healthy individuals, it will display symptoms of aging in the underlying living cells in older subjects. The area of corneocytes, which make up the stratum corneum, is proportional to the time taken for the keratinocyte to differentiate and move from the basal layer to the stratum corneum. In aged skin, the time taken to move through the epidermis increases, and corneocytes become larger. The surface can develop fine lines and become dry and scaly (senile xerosis). As aging progresses, the surface area of corneocytes increases, and thus this value can be measured to determine the effectiveness of an anti-aging treatment (i.e., to decrease the transit time and corneocyte surface area). In the present example, treatment of facial skin with a facial skin patch or mask of the invention containing 0.3% CoQ_{10}, once or twice daily for 7 days, will yield a significant decrease in the corneocyte area over time compared to treatment with a patch or mask coated or imbued with a delivery vehicle or carrier alone.

Additional advantages and modifications of the invention disclosed herein will be apparent to those persons skilled in the art. Accordingly, the invention is not limited to the specific details or illustrated examples described herein, except as provided by the appended claims.